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Patent application No. Demande de brevet nº Patentanmeldung Nr.

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Method for hla typing

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Method for HLA typing

The present invention relates to a method for HLA typing by the unambiguous determination of short DNA sequence elements (2-6 bases) at a given position simultaneously on both parental alleles at a selected number of positions in HLA genes, comprised of the steps for each position of a) hybridising a combination of oligonucleotides (primers) complementary to all known sequence variants to a DNA strand upstream of a given position; b) carrying out a primer extension reaction with at least one of the four dNTP substrates substituted by a terminating analog; c) analysing the products by mass spectrometry, with the resulting masses allowing unambiguous identification of the used primers and the added bases. This method is particularly well suited for DNA-based HLA typing and in combination with a suitable selection of sites tested, it is superior in ease of operation to conventional HLA typing methods.

The most important of the genome projects, the complete sequence of the human genome, is finished. This project reveals the complete sequence of the 3 billion bases and the relative positions of all estimated 30.000 genes in this genome. Having this sequence opens unlimited possibilities for the elucidation of gene function and interaction of different genes. In recent years a systematic effort (SNP consortium) has been underway to identify single nucleotide polymorphisms (SNPs) throughout the human genome and so far several million of these differences between different human beings have been identified (dbSNP contained 5.5 million SNPs in October 2003).

Matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI) has revolutionized the mass spectrometric analysis of biomolecules (Karas, M. & Hillenkamp, F. Anal. Chem. 60, 2299-2301 (1988)). The field of DNA analysis by mass spectrometry was recently extensively reviewed by Tost and Gut (Mass Spectrometry Reviews, 21, 388-418 (2002)) and Sauer and Gut (Journal of Chromatography B, 782, 73-87, (2002)). MALDI has been applied to the analysis of DNA in variations that range from the analysis of PCR products to approaches using allele-specific termination to single nucleotide primer extension reactions and sequencing (Liu, Y.-H., et al. Rapid Commun. Mass Spectrom. 9, 735-743 (1995);

Ch'ang, L.-Y., et al. Rapid Commun. Mass Spectrom. 9, 772-774 (1995); Little, D.P., et al. J. Mol. Med. 75, 745-750 (1997); Haff, L. & Smirnov, I.P. Genome Res. 7, 378-388 (1997), Fei, Z., Ono, T. & Smith, L.M. Nucleic Acids Res. 26, 2827-2828 (1998); Ross, P., Hall, L., Smirnov, I. & Haff, L. Nature Biotech. 16, 1347-1351 (1998); Ross, P.L., Lee, K. & Belgrader, P. Anal. Chem. 69, 4197-4202 (1997); Griffin, T.J., Tang, W. & Smith, L.M. Nature Biotech. 15, 1368-1372 (1997); Köster, H., Higgins, G.S & Little, D.P. US Patent 6,043,031). These methods are used to genotype previously identified mutations, SNPs, or insertion/deletions (indels). Spin column purification and/or magnetic bead technology, reversed-phase purification, or ion-exchange resins are frequently applied prior to mass spectrometric analysis.

The GOOD assay (IG Gut et S. Beck: US 6,268,812; IG Gut et al: US 6,503,710) is a method for SNP genotyping that uses MALDI mass spectrometry for detection (Sauer et al. 28, e13 and e100 (2000)). Allele-distinction is based on primer extension. In order to make products more amenable to MALDI analysis a substantial part of the primer is removed prior to mass spectrometric analysis. A further element that is included is charge tagging. This means that the final product is conditioned such that it carries either a single positive or a single negative charge. Generally this is achieved by alkylation of a phosphorothicate backbone and in some instances including a quaternary ammonium group to the penultimate base of the primer. The attachment of the quaternary ammonium group gives options for the design of multiplexes - individual SNPs can be moved up or down in the mass spectrum to achieve optimal resolution and separation.

The major histocompatibility complex (MHC) of humans is a cluster of genes on chromosome 6p21. It is of greatest importance as many diseases show association with genes in this region of the genome. All human leukocyte antigen (HLA) coding genes are found in the MHC. The HLA genes are highly variable and implicated in tissue transplantation, immunity and autoimmune disease such as diabetes, psoriasis, lupus, Crohn's disease, colitis, arthritis, and others. The HLA class I genes are HLA-A, HLA-B, HLA-C, The HLA class II genes are HLA-DR, HLA-DQ, HLA-DP,....





HLA typing methods differ dramatically in their approaches. Serological tests can be carried out but have only limited resolution. In the last 15 years the DNA sequence of the MHC has been extensively studied and high resolution typing now makes use of a wealth of DNA sequence information. Methods for DNA based HLA typing range from SSA (sequence specific amplification) where combinations of primers that are specific for different alleles are used to carry out PCR (US 5,545,526). Primers are combined in a way that the sizing of the PCR products allows unambiguous assignment of present base combinations. Multiple combinations are used to identify HLA types. The procedure works its way through a tree of combinations starting with a grouping into rough classes from where on further tests are carried out with specific reagents to subdivide in a class. This method is also known as SSP (sequence specific primers). An alternative method is termed SSOP (sequence specific oligonucleotide probes; US 6,503,707). Here a locus specific PCR is carried out followed by hybridisation with sequence specific oligonucleotide probes. As sequencing technology (and in particular the software for sequence calling) has dramatically improved over the last decade it now is also possible to gain a good degree of identification of HLA types by sequencing (WO 98/35059). Effectively a locus-specific PCR product is sequenced. Problems that arise here are that heterozygous individuals occasionally give rise to ambiguous haplotype calls that can not be resolved (Robinson, J.; Waller, M.J.; Marsh, St.G.E.: "Exon Identities and Ambiguous Typing Combinations"; IMGT/HLA Database; October 2003). The inclusion of allele-specific PCR helps achieve certainty. Resolution requires multiple products per locus to be generated and sequenced. However, as sequencing results can be very convoluted the interpretation in absence of allele-specific PCR can be cumbersome. All together the sequence-based typing requires many iterations in application. Reference strand mediated conformation analysis (RSCA) is a method used to study samples that potentially have a previously unknown sequence in their HLA (Correl et al., Tissue Antigens 56, 82-86, 2000). For a recent review for the reasoning of HLA typing as well as methodological advances see Petersdorf et al. (Tissue Antigens, 61, 1-11, 2003).



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The object of the present invention is a method for HLA typing by the unambiguous determination of short DNA sequence elements (2-6 bases) simultaneously on both parental alleles at a selected number of positions in HLA genes, comprised of the steps for each position of a) hybridising a combination of oligonucleotides (primer pool) complementary to all known sequence variants to a DNA strand upstream of a given position; b) carrying out a primer extension reaction with at least one of the four dNTP substrates substituted by a terminating analog; c) analysing the products by mass spectrometry, with the resulting masses allowing unambiguous identification of the used primers and the added bases.

In the present invention:

- "HLA" means the human leukocyte antigen locus on chromosome 6p21, consisting of HLA genes (HLA-A, HLA-B, HLA-C, HLA-DRB1,...) that are used to determine the degree of matching, for example, between a recipient and a donor of a tissue graft.
 - "HLA typing" means the identification of a known HLA allele of a given locus (HLA-A, HLA-B, HLA-C, HLA-DRB1,...).
- "HLA allele" means a nucleotide sequence within a locus on one of the two parental chromosomes.
 - "HLA-A" means the DNA sequence of exons 2 and 3 of the HLA-A gene.
 - "HLA-B" means the DNA sequence of exons 2 and 3 of the HLA-B gene.
 - "HLA-DRB1" means the DNA sequence of exon 2 of the HLA-DRB1 gene.
- "Polymorphism" means individual positions in a DNA sequence that exist in different variants.
 - "Haplotype" means the DNA sequence of one of the two alleles in a give region of the genome.



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- "Mini-haplotype" means 2-6 contiguous bases on one parental allele.
- "Primer pools" or "pools of primers" means sets of primers that are used in one primer extension reaction. For each known HLA allele at least one primer is in the pool that is completely complementary in sequence. This assures perfect annealing. Mismatches that are more than 4 bases from the 3'end of the primer do not affect the results of the GOOD assay, as all of those bases are removed by 5'phosphodiesterase after the primer extension reaction. Primers of the pool containing mismatches in the last few bases are not extended by the DNA polymerase and thus not observable.
- "MALDI mass spectrometer" means a mass spectrometer that uses matrixassisted laser desorption/ionization for the volatilisation of a sample and time-offlight analysis for mass separation.
 - "Subgroup" means alleles, which are identical after the mini-haplotyping of the first set of selected positions. For the high resolution typing we resolve subgroups generated with 10 mini-haplotyping reactions. The criteria for resolving subgroups are: a) they still contain alleles with different two-digit types, b) subgroups with more than four alleles, and c) subgroups with frequent alleles (see list below).
- 20 Here we show a methodology for the determination of sequence motifs of 2-6 bases in very polymorphic regions of genomes. In principle this methods equates to the determination of mini-haplotypes of 2-6 bases. The individual parental minihaplotypes can be determined in one reaction without ambiguities. This methodology is applied to a chosen set of positions for HLA typing of HLA-A, HLA-B, and HLA-DRB1. The sets disclosed here have different purposes. First sets 25 of 19, 19, and 10 positions are suggested to distinguish a maximum of HLA alleles in HLA-A, HLA-B, and HLA-DRB1, respectively, with respect to differentiating alleles that are frequent in the general population from ones that are rare. The frequent alleles that were screened for are A*0101, A*0201, A*0301, A*2301, A*2402, A*2902, A*3001 and A*3002 for HLA-A, B*0702, B*0801, B*1302, 30 B*1501, B*1801, B*3501, B*3503, B*4001, B*4402, B*4403, B*5101 and B*5701 for HLA-B, and DRB1*0101, DRB1*0301, DRB1*0401, DRB1*0701,





DRB1*1101, DRB1*1104, DRB1*1302 and DRB1*1501 for HLA-DRB1. This set of markers provides unambiguous identification of frequent HLA alleles with 93.4 - 100 % certainty in HLA-A, 97.6 - 100 % in HLA-B, and 97.2 - 100 % in HLA-DRB1.

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A second set of 10 positions each in HLA-A, HLA-B, and HLA-DRB1, respectively are described that provide a maximum number of subgroups, that can then be further resolved by the addition of a set of subgroup specific positions. Again the ten positions in each locus were chosen on the basis of providing best distinction between the frequent HLA alleles listed above from the rest of the HLA alleles (rare). This resulted in groups containing 2-30 HLA alleles depending on the locus. Within each group a number of positions can be tested to provide resolution between the HLA alleles within the group. The number of positions that have to be additionally analysed range from 1-25 in order to achieve 4-digit resolution. With this technology HLA typing can be carried out at a substantially reduced cost with a proven high-throughput detection platform (MALDI mass spectrometry).

In a preferred embodiment of the method of the invention, the DNA strand of step a) is produced by a DNA replication procedure such as PCR or rolling circle replication.

A set of locus-specific PCR reactions for the selective amplification of each locus is described by the International Histocompatibility Working Group, Technical Manuals (Hurly, Fernandes-Vina, Gao, Middleton, Noreen, Ren and Smith; www.ihwg.org/tmanual/Tmcontents.htm).

In a very preferred embodiment of the method of the invention, a combination of primers (pools of primers) contains slightly varying sequences so that all known sequences of the HLA alleles are accommodated by a perfectly matching primer.

The pool of primers guarantees that at least one primer is perfectly matched. The hybridised oligonucleotides of the primer pool are extended onto a polymorphic position. A requirement is that the added base together with the base composition of the primer gives a unique mass. The detection of this mass in the mass spectrometric profile indicates the presence of a sequence containing both the complementary sequence of the primer and the added base. In order to make all

primers of a primer pool distinguishable by mass it is possible to add different mass shifting agents to the primers. The easiest way to accomplish this is by using charge/mass tagging technology such as is used in the GOOD assay. The penultimate base from the 3'end of the primer is amino-modified and used to add tags via NHS-ester chemistry. The pools of primers of course contain primers that sometimes differ by as little as one base. Sequences identical in base content can still be distinguished by the suitable selection of mass tags. Also, we have found that a primer carrying a mismatch in the last eight bases from the 3'end even if it anneals is not extended by the polymerase and thus screened out. This might be due to insufficient hybridisation or a resistance of the DNA polymerase to attach or extend when a mismatch is present. We thus make use of two effects for our minihaplotyping: 1) allele-specific hybridisation and 2) allele-specific primer extension. Mismatches that are further than four bases away from the 3'end of the extension primer do not result in increased complexity of the mass spectra as they are removed in the 5'phosphodiesterase digestion step of the GOOD assay.

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In a preferred embodiment of the method of the invention, mass shifting tags are added to the individual primers sequences of a primer pool to make them uniquely distinguishable once the terminating base is added.

In another preferred embodiment of the method of the invention, termination products for know alleles are generated by extending the perfectly hybridised primer with a combination of dNTPs and ddNTPs or analogues thereof with a DNA polymerase to generate specific termination products to make them uniquely-distinguishable by their mass.

In a preferred embodiment of the method of the invention, the GOOD assay is used.

It typically applies single base primer extension, thus only the four terminating bases (ddNTPs) or synthetic analogues with the same qualities in terms of DNA polymerase tolerance are used for primer extension. α-S-ddNTPs are very suitable analogues.

In a preferred embodiment of the method of the invention, mass spectrometry, in 30 particular MALDI or ESI mass spectrometry is used for analysis of the masses of products. For HLA typing a set of said mini-haplotyping assays has to be carried out to achieve sufficient information content.

For HLA typing of HLA-A the preferred set of assays are those of positions 98, 414, 539, 282, 571, 368, 256, 292, 238, 270, 453, 527, 502, 81, 268, 559, 92, 123 and 396 (according to the numbering of the HLA-A gene starting at cDNA sequence position 1 of exon 1; see Figure 1). This results in medium resolution HLA typing. The input criteria for the selection are the frequency of HLA alleles. Some HLA types are identified unambiguously.

For HLA typing of HLA-B accordingly the following positions are preferably analysed by mini-haplotyping assays to achieve medium resolution: 539, 419, 559, 412, 272, 362, 302, 363, 206, 369, 259, 97, 583, 292, 222, 527, 418, 435 and 571 (according to the numbering of the HLA-B gene starting at cDNA sequence position 1 of exon 1; see Figure 2).

For HLA typing of HLA-DRB1 accordingly the following positions are preferably analysed by mini-haplotyping to achieve medium resolution: 125, 196, 197, 227, 261, 286, 299, 308, 341 and 345 (according to the numbering of the HLA-DRB1 gene starting at cDNA sequence position 1 of exon 1; see Figure 3).

414, 539, 282, 571, 368, 256, 292, 238 and 270 (according to the numbering of the HLA-A gene starting at cDNA sequence position 1 of exon 1; see Figure 4) are used for mini-haplotyping to generate sub-groups (HLA-A_A, HLA-A_B, HLA-A_C, HLA-A_D, HLA-A_E, HLA-A_F, HLA-A_G, HLA-A_H, HLA-A_I, HLA-A_I, HLA-A_I, HLA-A_N, and HLA-A_O; see Table I). Positions 224, 268, 376, 502, 561, and 616 are preferably analyzed to proceed

In a preferred embodiment for high resolution HLA typing of HLA-A positions 98,

Positions 224, 268, 376, 502, 561 and 616 are preferably analysed to resolve subgroup HLA-A_A (sequences identical over exons 2 and 3 for alleles A*29010101 and A*29010102); positions 126 and 526 to resolve subgroup HLA-A_B; positions 81, 90, 92, 212, 214, 257, 265, 299, 302, 404, 420, 427, 453, 485, 489 and 502 to resolve subgroup HLA-A_C (sequences identical over exons 2 and 3 for alleles A*24020101, A*24020102L, A*240203, A*2409N and A*2411N); positions 160, 200, 362 and 524 to resolve subgroup HLA-A_D; positions 180, 299,

positions 160, 200, 362 and 524 to resolve subgroup HLA-A_D; positions 180, 299, 301, 302, 346, 418, 453, 517, 524, 526, 527, 557, 559 and 560 to resolve subgroup HLA-A_E; positions 299, 301, 302, 341 and 583 to resolve subgroup HLA-A_F;



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positions 127, 341, 399, 480, 502, 503, 524, 526, 527, 553, 559, 560 and 565 to resolve subgroup HLA-A_G; positions 228, 233, 463, 519, 530 and 583 to resolve subgroup HLA-A_H; positions 102, 275, 317, 362, 418, 419, 497, 524, 555, 595 and 618 to resolve subgroup HLA-A_I (sequences identical over exons 2 and 3 for alleles A*680102 and A*6811N); positions 92, 331, 453, 524, 559, 560 and 564 to resolve subgroup HLA-A_J; positions 78, 81, 123, 125, 142, 144, 194, 268, 294, 324, 355, 362, 396, 403, 419, 453, 456, 477, 493, 517, 524, 526, 527, 559 and 560 to resolve subgroup HLA-A_K (sequences identical over exons 2 and 3 for alleles A*02010101, A*02010102, A*020108, A*0209, A*0243N and A*0266); positions 113, 299, 301, 302, 308, 311, 523, 524 to resolve subgroup HLA-A_L; positions 171, 363, 498 and 559 to resolve subgroup HLA-A_M; position 299 to resolve subgroup HLA-A_O.

TABLE I

Subgroups of	Alleles of Subgroups	Positions to resolve
HLA-A		Subgroups
HLA-A A	A*29010101, A*29010102, A*290201, A*290202,	224 269 276 502 561
I ILLA-A_A		224, 268, 376, 502, 561, 616
	A*2904, A*2906, A*2908N, A*2909	
HLA-A_B	A*3002, A*3009, A*3012	126, 526
HLA-A_C	A*24020101, A*24020102L, A*240202, A*240203,	81, 90, 92, 212, 214, 257, 265, 299, 302, 404, 420,
	A*240204, A*2404, A*2405, A*2408, A*2409N,	427, 453, 485, 485, 489,
	A*2411N, A*2420, A*2421, A*2425, A*2426, A*2427,	502
ļ	A*2429, A*2432, A*2435, A*2436N, A*2437, A*2438,	
	A*2439	
HLA-A_D	A*0206, A*0214, A*0221, A*0251, A*0257	160, 200, 362, 524
HLA-A_E	A*250101, A*250102, A*2601, A*2604, A*2605,	180, 299, 301, 302, 346,
}	A*2609, A*2610, A*2611N, A*2612, A*2614, A*2615,	418, 453, 517, 524, 526, 527, 557, 559, 560
	A*2617, A*2618, A*6603	027,007,007,000
HLA-A_F	A*2502, A*2613, A*6601, A*6602, A*6604	299, 301, 302, 341, 583
HLA-A_G	A*110101, A*110102, A*1102, A*1103, A*1104,	127, 341, 399, 480, 502,
	A*1105, A*1107, A*1109, A*1112, A*1113, A*1114,	503, 524, 526, 527, 553, 559, 560, 565
	A*1115	339, 300, 303
HLA-A_H	A*3301, A*330301, A*330302, A*3304, A*3305,	228, 233, 463, 519, 530,
	A*3306, A*3307	583
HLA-A_I	A*680101, A*680102, A*680103, A*6807, A*6811N,	102, 275, 317, 362, 418,
	A*6812, A*6816, A*6817, A*6819, A*6821, A*6822,	419, 497, 524, 555, 595, 618
	A*6823, A*6824	,
HLA-A_J	A*2301, A*2303, A*2305, A*2306, A*2307N,	92, 331, 453, 524, 556,
	A*2308N, A*2310, A*2413	560, 564
HLA-A_K	A*02010101, A*02010102, A*020102, A*020103,	78, 81, 123, 125, 142,
•	A*020104, A*020105, A*020106, A*020107,	144, 194, 268, 294, 324,
	A*020108, A*020109, A*0204, A*0209, A*0216,	355, 362, 396, 403, 419, 453, 419, 453, 456, 477,
	A*0224, A*0225, A*0226, A*0229, A*0230, A*0231,	493, 517, 524, 526, 527,
	A*0232N, 0A*0240, A*0242, A*0243N, A*0258,	559, 560
	A*0259, A*0260, A*0264, A*0266, A*0267, A*0253N	
HLA-A_L	A*3201, A*3203, A*3206, A*7401, A*7402, A*7403,	113, 299, 301, 302, 308,
	A*7408, A*7409	311, 523, 524
HLA-A_M	A*010101, A*010102, A*0103, A*0104N, A*0108,	171, 363, 498, 559
_	A*0109	, , , , , , ,
HLA-A N	A*03010101, A*03010102, A*0303N, A*0304, A*0305,	376, 426, 527, 555, 557,
	A*0306, A*0307, A*0311N	595
HLA-A O	A*2504, A*2608	299
	· · · · · · · · · · · · · · · · · · ·	

In a preferred embodiment for high resolution, HLA typing of HLA-B positions 539, 419, 559, 412, 272, 362, 302, 363, 206 and 369 (according to the numbering of the HLA-B gene starting at cDNA sequence position 1 of exon 1; see Figure 5) are used for mini-haplotyping to generate sub-groups (HLA-B A, HLA-B B, HLA-B C, HLA-B_D, HLA-B_E, HLA-B_F, HLA-B_G, HLA-B_H, HLA-B_I, HLA-B_J, HLA-B K, HLA-B L, HLA-B M, HLA-B N, HLA-B O, HLA-B P, HLA-B Q, HLA-B_R, HLA-B_S, HLA-B_T, HLA-B_U, HLA-B_V, HLA-B_W, HLA-B_X, HLA-B Y, HLA-B Z, HLA-B AA, HLA-B AB and HLA-B AC; see Table II). Positions 259, 341 and 473 are preferably analyzed to resolve subgroup HLA-B A (sequences identical over exons 2 and 3 for alleles B*0801 and B*0819N); positions 106, 144, 222, 259, 273, 311, 313, 418, 445, 493, 528 and 540 to resolve subgroup HLA-B B (sequences identical over exons 2 and 3 for alleles B*44020101, B*44020102, B*4419N and B*4427); positions 319, 416, 545 and 572 to resolve subgroup HLA-B C; positions 106, 131, 165, 215, 243, 277, 292, 322, 481, 582, 603 and 616 to resolve subgroup HLA-B D; positions 106, 146, 165, 181, 238, 259, 263, 292, 328.1/329(insert for B*1579N), 379, 435, 453, 463, 485, 526, 571, 572 and 583 to resolve subgroup HLA-B E (sequences identical over exons 2 and 3 for alleles B*15010101 and B*15010102); positions 142, 171, 255, 257, 395, 430, 544, 566 and 572 to resolve subgroup HLA-B F; positions 117, 247, 248, 277, 345, 418, 489 and 527 to resolve subgroup HLA-B G (sequences identical over exons 2 and 3 for alleles B*270502, B*270504 and B*2713); positions 134, 141, 200, 213, 259, 304 and 527 to resolve subgroup HLA-B H; positions 83, 141, 211, 222, 242, 322, 404, 414, 435, 463, 502, 527, 544, 571, 572 and 583 to resolve subgroup HLA-B_I (sequences identical over exons 2 and for alleles B*510101, B*510105, B*5111N, B*5130 and B*5132); positions 103, 142, 222, 243, 259, 292, 477, 486 and 499 to resolve subgroup HLA-B_J (sequences identical over exons 2 and 3 for alleles B*400101 and B*400102); positions 103, 259, 292, 295, 527 and 583 to resolve subgroup HLA-B K (sequences identical over exons 2 and 3 for alleles B*180101 and B*1817N); positions 320 and 500 to resolve subgroup HLA-B L; positions 311, 527 and 583 to resolve subgroup HLA-B M; positions 119, 292, 259, 319, 425, 527, 546 and 583 to resolve subgroup HLA-B_N (sequences identical over exons 2 and 3 for alleles B*350101, B*3540N and B*3542); positions 97, 142, 245 and 527 to resolve subgroup HLA-B_O; positions 97 and 175 to resolve subgroup HLA-B P; positions

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TABLE II

6.	Len 1	· · · · · · · · · · · · · · · · · · ·
	Alleles of the subgroup	Positions to resolve
HLA-B		<u>Subgroups</u>
HLA-B_A	B*0801, B*0808N, B*0810, B*0818, B*0819N	259, 341, 473
HLA-B_B	B*44020101, B*44020102S, B*440202, B*440203,	106, 144, 222, 259, 273
İ	B*4405, B*4411, B*4412, B*4419N, B*4422, B*4423N,	311, 313, 418 445, 493,
	B*4424, B*4425, B*4427, B*4433, B*4434, B*4435	528, 540
HLA-B_C	B*4415, B*4501, B*4503, B*4504, B*4505	319, 416, 545, 572
HLA-B_D	B*070201, B*070202, B*070203, B*070204, B*0703,	106, 131, 165, 215, 243,
	B*0716, B*0721, B*0722, B*0723, B*0729, B*0730,	277, 292, 322, 481, 582,
	B*0733, B*0735	603,616
HLA-B_E	B*15010101, B*15010102, B*150102, B*150103,	106, 146, 165, 181, 238,
	B*150104, B*1512, B*1514, B*1515, B*1519, B*1528,	259, 263, 292,
	B*1533, B*1534, B*1538, B*1560, B*1570, B*1571,	328.1/329, 379, 435,
	B*1575, B*1578, B*1579N, B*1581, B*1582	453, 463, 485, 526, 571,
		572,583
HLA-B_F	B*440301, B*4413, B*4426, B*4429, B*4430, B*4432,	142, 171, 255, 257, 395,
	B*4436, B*4437, B*4438, B*4439	430, 544, 566 , 572
HLA-B_G	B*2703, B*270502, B*270503, B*270504, B*270505,	j
	B*270506, B*2709, B*2710, B*2713, B*2716, B*2717	418, 489 , 527
HLA-B_H	B*5107, B*520101, B*520102, B*520103, B*520104,	1
·	B*5203, B*5204, B*5205	304,527
HLA-B_I	B*510101, B*510102, B*510103, B*510104, B*510105,	83, 141, 211, 222, 242,
	B*510201, B*510202, B*5103, B*5109, B*5111N,	322, 404, 414, 435, 463,
1	B*5112, B*5114, B*5118, B*5119, B*5123, B*5124,	
	B*5126, B*5127N, B*5128, B*5130, B*5132, B*5133	583
HLA-B_J	B*400101, B*400102, B*400103, B*4010, B*4011,	103, 142, 222, 243, 259,
	B*401401, B*401402, B*401403, B*4022N, B*4025,	1
1 1	B*4043	
HLA-B_K	B*180101, B*180102, B*1803, B*1804, B*1805,	103, 259, 292, 295, 527,
1 1	B*1811, B*1812, B*1815, B*1817N	583
HLA-B_L	B*570101, B*5706, B*5708	320, 500
HLA-B_M	B*3527, B*5301, B*5302, B*5306, B*5308	311, 527, 583
HLA-B_N	B*350101, B*350102, B*3507, B*3510, B*3511,	
1	B*3521, B*3524, B*3529, B*3540N, B*3541, B*3542,	
1	B*5305	, - · · · , - · · ·
HLA-B_O	B*5501, B*5502, B*5505, B*5510, B*5516	97, 142, 245, 527
	B*5401, B*5402, B*5507	97, 175
	,	//g I/J





HLA-B_Q	B*3910, B*670101, B*670102	246, 277
HLA-B_R	B*3803, B*390201, B*390202, B*3913, B*3923	246, 292, 311, 503
HLA-B_S	B*3801, B*380201, B*380202, B*3804, B*3805, B*3809	103, 261, 309, 311, 474
HLA-B_T	B*390101, B*390103, B*390104, B*3904, B*3905,	97, 103, 106, 243, 259,
	B*3912, B*3922, B*3925N, B*3926	292, 404 , 524
HLA-B_U	B*3503, B*3513, B*3536	259,320
HLA-B_V	B*0734, B*5504	106
HLA-B_W	B*4047, B* 4431	97
HLA-B_X	B*4002, B*4027, B*4029, B*4035, B*4040, B*4045	97, 106, 257, 418, 463
HLA-B_Y	B*400104, B*4004	106
HLA-B_Z	B*4012, B*4046, B*4803	106, 144
HLA-B_AA	B*2703, B*270502, B*270503, B*270504, B*270505,	117, 247, 248, 283, 345,
	B*270506, B*2709, B*2710, B*2713, B*2716, B*2717	418, 489, 527
HLA-B_AB	B*1562, B*4802	106
HLA-B_AC	B*1302, B*1308	548
	<u> </u>	

246 and 277 to resolve subgroup HLA-B_Q; positions 246, 292, 311 and 503 to resolve subgroup HLA-B_R; positions 103, 261, 309, 311 and 474 to resolve subgroup HLA-B_S; positions 97, 103, 106, 243, 259, 292, 404 and 524 to resolve subgroup HLA-B_T (sequences identical over exons 2 and 3 for alleleles B*390101 and B*390103); positions 259 and 320 to resolve subgroup HLA-B_U; position 106 to resolve HLA-B_V; positions 97 to resolve HLA-B_W; positions 97, 106, 257, 418 and 463 to resolve HLA-B_X; position 106 to resolve HLA-B_Y; positions 106 and 144 to resolve HLA-B_Z; positions 117, 247, 248, 283, 345, 418, 489, and 527 to resolve HLA-B_AA; positions 106 to resolve HLA-B_AB; positions 548 to resolve HLA-B_AA.

In a preferred embodiment, the method for HLA typing resolves groups A-P of HLA-DRB1.

For high resolution, HLA typing of HLA-DRB1 positions are: 125, 196, 197, 227, 261, 286, 299, 308, 341 and 345 (according to the numbering of the HLA-DRB1 gene starting at DNA sequence position 1 of exon 1; see Figure 6) are used for mini-haplotyping to generate sub-groups (HLA-DRB1_A, HLA-DRB1_B, HLA-DRB1_C, HLA-DRB1_D, HLA-DRB1_E, HLA-DRB1_F, HLA-DRB1_G, HLA-DRB1_H, HLA-DRB1_I, HLA-DRB1_J, HLA-DRB1_K, HLA-DRB1_L, HLA-DRB1_M, HLA-DRB1_N, HLA-DRB1_O, HLA-DRB1_P; see Table III).

In a very preferred embodiment, positions 123, 174, 250, 278 and 317 are analysed to resolve subgroup HLA-DRB1 A; positions 192, 203, 256 and 259 to resolve subgroup HLA-DRB1_B; 256, 260, 317 and 351 to resolve subgroup HLA-DRB1_C; positions 155, 204, 233, 239, 256, 304, 357 and 366 to resolve subgroup HLA-DRB1_D; positions 122, 171, 257 and 317 to resolve subgroup HLA-DRB1 E; positions 164, 167, 171, 230, 235, 306, 317, 321 and 337 to resolve subgroup HLA-DRB1_F; positions 164, 257, 266 and 303 to resolve subgroup HLA-DRB1_G; positions 164, 181, 188, 220, 229, 256, 266, 317 and 318 to resolve subgroup HLA-DRB1_H; position 257 to resolve subgroup HLA-DRB1 I; positions 181, 239 and 357 to resolve subgroup HLA-DRB1_J; positions 122, 144, 239, 303, 317, 318 and 321 to resolve subgroup HLA-DRB1 K (sequences identical over exons 2 and 3 for alleles DRB1*110101 and DRB1*110102); positions 118, 161, 257, 260, 318 and 321 to resolve subgroup HLA-DRB1 L; positions 165, 257, 293 and 303 to resolve subgroup HLA-DRB1 M (sequences identical over exons 2 and 3 for alleles DRB1*120101 and DRB1*1206); positions 177, 240, 256, 257 and 357 to resolve subgroup HLA-DRB1_N; positions 150 175, 230, 236 and 321 to resolve subgroup HLA-DRB1 O (sequences identical over exons 2 and 3 for alleles DRB1*150101 and DRB1*1513); positions 115, 220 and 317 to resolve subgroup HLA-DRB1_P.

Another object of the invention is a kit to carry out the procedure. It consists of pooled combinations of primers. The primers that are used in the pools for HLA-A, HLA-B, and HLA-DRB1 and the masses of the genotyping products are listed in Tables IV, V, and VI respectively. CT refers to the mass shifting mass tag that is attached to that primer of the pool.

Another object of the invention is the use of the method of the invention for screening of tissue donors.

In a preferred embodiment, the use is for bone marrow donors in registries for screening of frequent and rare HLA types.

Still another object of the invention is the use of the primers represented in Table IV, V and VI to carry out HLA typing.

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TABLE III

Subgroups of	Alieles of Subgroups	Positions to resolve
HLA-DRB1	Amoles of bacgroups	Subgroups
HLA-	DRB1*070101, DRB1*070102, DRB1*0703, DRB1*0704,	123 174 250 317
DRB1_A	DRB1*0705, DRB1*0707	123, 174, 230, 317
HLA-	DRB1*040101, DRB1*040102, DRB1*0409, DRB1*0426,	192, 203, 256, 259
DRBI B	DRB1*0433	
HLA-	DRB1*0404, DRB1*0410, DRB1*0423, DRB1*0440,	256 260 317 351
DRB1_C	DRB1*0444	250, 200, 517, 551
HLA-	DRB1*040501, DRB1*040502, DRB1*040503,	155, 204, 233, 239,
DRB1_D	DRB1*040504, DRB1*0408, DRB1*0429, DRB1*0430,	256, 304, 357, 366
	DRB1*0445, DRB1*0448	
HLA-	DRB1*1402, DRB1*1409, DRB1*1413, DRB1*1446,	122, 171, 257, 317
DRB1_E	DRB1*1447, DRB1*1448	•
HLA-	DRB1*130101, DRB1*130102, DRB1*130103,	164, 167, 171, 230,
DRB1_F	DRB1*1315, DRB1* 1327,	235, 306, 317, 321,
		337
HLA-	DRB1*130201, DRB1*130202, DRB1*1331, DRB1*1339,	164, 257, 266, 303
DRB1_G	DRB1*1341	
HLA-	DRB1*030101, DRB1*030102, DRB1*0307, DRB1*0312,	164, 181, 188, 220,
DRB1_H	DRB1*0313, DRB1*0315, DRB1*0316, DRB1*0318,	229, 256, 266, 317,
	DRB1*0322, DRB1*0323	318
HLA-	DRB1*1137, DRB1*1425	257
DRB1_I		
HLA-	DRB1*110401, DRB1*110402, DRB1*1143, DRB1*1146	181, 239, 357
DRB1_J	·	
HLA-	DRB1*110101, DRB1*110102, DRB1*110103,	122, 144, 239, 303,
DRB1_K	DRB1*110104, DRB1*110105, DRB1*112701,	317, 318, 321
	DRB1*112702, DRB1*1130, DRB1*1139	
HLA-	DRB1*1117, DRB1*140101, DRB1*140102, DRB1*1408,	118, 161, 257, 260,
DRB1_L	DRB1*1426, DRB1*1438, DRB1*1439	318, 321
HLA-	DRB1*120101, DRB1*120102, DRB1*1206, DRB1*1207,	165, 257, 293, 303
DRB1_M	DRB1*1208, DRB1*1209	·
HLA-	DRB1*080101, DRB1*080102, DRB1*080201,	177, 240, 256, 257,
DRB1_N	DRB1*080202, DRB1*080203, DRB1*0807, DRB1*0811	357
HLA-	DRB1*150101, DRB1*150103, DRB1*150105,	150 175, 230, 236,
DRB1_O	DRB1*1503, DRB1*1506, DRB1*1509, DRB1*1513	321
HLA-	DRB1*010101, DRB1*0105, DRB1*0107, DRB1*0111	115, 220, 317
DRB1_P		
L	I	<u>. </u>





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	TABLE IV								
	No.	. Name	Comuna	CT.	Primer Masses	A	С	G	Ť
			Sequence TGCTCGCCCCAGGCTCCspC^spA	To		4405.4	14404.0		
		HLAA_812_1f20	TGCTCGCCCCAGGCTCCspC spA	1 6	1098,1 1113,1	1425,1	1401,3 1416,3		
				۱ Ť	1110,1		1410,3	1452,4	
		HLAA_921_1f20	AGGCTCCCACTCCATGAGspC^spT	0	1129,1	1456,4	 		-
		HLAA 922 1f20	AGGCTCCCAMTCCATGAGspG^spT	0	1169,1	1496,4		1512,4	-
	5	HLAA_923_1f20	AGGCTCTCASTCCATGAGspG^spT	0	1169,1	1496,4		1512,4	-
		111 44 004 4600	00407004700470						
5	 	HLAA_981_1f20 HLAA_982_1f20	CCACTCCATGAGGTATTTspC^spA	10	1113,1		1416,3	-	
	- -	TILAA_30Z_11ZU	CCACTCCATGAGGTATTTspC^spT	10	1104,1	1431,4	1407,3		1422,3
	8	HLAA 1231 2r20	GCGATGAAGCGGGGCTCspCspT^spC	0	1510,5			1853,8	
	9	HLAA_1232_2r20	GCGATGAAGCGGGGCTCspTspC^spC	-28			<u> </u>	1000,0	
	10	HLAA_1233_2r20	GCGATGAAGCGGGGCTTspCspC^spC	0	1408,4	-	-	1751,6	-
	11	HLAA_1234_2r20	GMGATGAAGCGGGGCTCspCspC^spC	0	1393,4	1720,7	-	1736,7	
	L								
	12	HLAA_2381_2r20	CTSGTCCCAATACTCCGspGspA^spC	0	1497,4	•	1800,6	·	-
10	13	HLAA 2382 2120	CYCGTCCCAATACTCCGspGspA^spC	0	1497,4		1800,6	•	-
	15	HI AA 2384 2#20	CTCGTCCCAATACTCCGspGspC^spT CTSGTCCCAATACTCAGspGspC^spC	0	1488,4	-	1791,6	-	1806,4
í	16	HLAA 2385 2r20	CYGGTCCCAATACTCAGspGspC*spC CYGGTCCCAATACTCCGspGspC*spC	10	1473,4 1473,4		1776,6		
	17	HLAA 2386 2r20	CMGGTCCCAATACTCCGspGspC^spC	Ö	1473,4	-	1776,6 1776,6	-	
	18	HLAA_2387_2r20	CYCGTCCCAATACTCCGspGspC^spC	ŏ	1473,4		1776,6		<u> </u>
							1110,0		
	19	HLAA_2561_1r19	CTTCATATTCCGTGTCTCspC^spT	0	1089,1	-	1392,3	1432,4	-
			CTTCACWTTCCGTGTCTCspC^spT	0	1089,1	-	1392,3	1432,4	-
15	21	HLAA 2563 1r19	CTTCACATKCCGTGTCTGspC^spA	0	1138,1	-	•	1481,4	•
''	23	HI AA 2565 4-10	CTTCACTTTCCGTGTGTTspC^spC CYTCACATTCCGTGTGTTspC^spC	Ö	1089,1	-	-	1432,1	•
ı	24	HLAA 2566 1r19	CTTCACATTCCGTGTGTTspC-spC CTTCACRTTCCGTGTCTCspC-spC	응	1089,1 1074,1		4277.0	1432,1	-
ı	25	HLAA 2567 1r19	CTTCASTTGCCGTGTCTCspC^spC	6	1074,1	-	1377,3 1377,3	1417,4	
Ī	26	HLAA_2568_1r19	CTTCAGTTKCCGTGTCTCspC^spC	ō	1074,1		1377,3	1417.4	
							,0	,	
ı	28	HLAA_2681_1f20	ATTGGGACCGGAACACACspG^spG	0	1154,1	1481,4	1457,3	-	-
ŀ	29	HLAA 2682 1120	ATTGGGACCTGCAGACACspG^spG	ō	1154,1	1481,4	1457,3	•	-
20 E	31	HI AA 2684 1620	ATTGGGACSAGGAGACACspG^spG ATTGGGACSGGGAGACACspG^spG	0	1154,1	1481,4	1457,3		-
20 F	32	HLAA 2685 1f20	ATTGGGACSAGGAGACACSpG*spG ATTGGGACSAGGAGACAGspG*spG	ö	1154,1 1194,1	1481,4 1521,4		-	
1			·	H	1104,1	1021,4			
	33	HLAA_2701_1r19	CTGTGAGTGGGCCTTCspA^spT	0	1113,1	1440.4	-		
ļ	34	HLAA_2702_1r19	CTGTGACTGGGCCYTCspA^spC	-14	1084,1	1411,4	-	1427,4	1402,4
-	35	HLAA_2703_1r19	CTGTGAGTGGSCCTTCspA^spC	-14	1084,1	1411,4	-	1427,4	
ŀ	36	HI AA 2024 4520	ACACCCAATCTCADCCCC	ليِّــا					
ŀ	37	HLAA 2822 1620	ACACGGAATGTGARGGGCspC^spA ACASGGAAAGTGAAGGCCspC^spA	္က	1098,1		1401,3		
,	38	HLAA 2823 1f20	ACACGGCAWGTGAAGGCCspC*spA	0	1098,1 1098,1		1401,3		
25	39	HLAA 2824 1f20	ACACGGAACGTGAAGGCCspC*spA	6	1098,1	-	1401,3 1401,3		
	40	HLAA 2825 1f20	ACACGGAATRTGAAGGCCspC^spA	ŏ	1098,1		1401,3		
ŀ	41	HLAA_2921_2f20	TGAAGGCCCACTCACAGspAspG^spT	-14	1498,4		1801,6	-	-
ŀ	42	HLAA 2922 2f20	TGAAGGCCCACTCACAGspGspC^spT	0	1488,4	<u>- ·</u>		1831,7	
ŀ	43	HI AA 2024 2020	TGAAGGSCCACTCACAGspAspT^spT	Ö	1589,6]	-	1932,9	
ŀ	45	HLAA 2925 2620	TGARGGCCCAGTCACAGspAspC^spT TGAAGGCCCASTCACAGspAspC^spT	9	1427,4		1775,6		
- 1		ULULU_ZIZU	TO THOSOCOASTCACAGSPASPC"Sp1	9	1427,4		1775,6	1815,7	
10	46	HLAA_3681_1f20	TCACACCATCCAGATAATspG^spC	0	1129,1	1456,4			
L	47	HLAA_3682_1f20	TCACACCATCCAGMTAATspG^spT	0			1447,1	1487.4	1462 3
L	48	HLAA_3683_1f20	TCACACCSTCCAGAGGATspG^spT	Ŏ		1471,6		1487,4	
L	49	HLAA_3684_1f20	TCACACCVTCCAGATGATspG^spT	0		1471,6		1487,4	
H	50	HI AA 2004 0.00	007007100000000						
L	201	11-WY 3901 XLX0	GCTGGTACCCGCGGAGspGspA^spG	0	1537,4	1		1880,7	

l			GCCGGTACCCGCGGAGspTspA^spA	0	1496,4	•		1839,7	-
ļ			GGTGGTACCCGYGCAGspGspA^spA	0	1496,4	•	-	1839,7	
			GGTGGTACCCGCAGAGspGspA^spA	0	1521,5	-	•	1864,8	1839
	54	HLAA_3965_2r20	GTTCATACCCGCGGAGspGspA^spA	0	1521,5	-	-	1864,8	1839
	55	HLAA_3966_2r20	GSTGGTACCCGCGGAGspGspA^spA	0	1521,5	-	-	1864,8	1839,
	56	HLAA 3967 2r20	GCCGGTACCCGCGGAGspGspA^spA	0	1521,5	1	-	1864,8	1839,
	57	HLAA_4141_1f20	CGCTTCCTCCGCGGGTATspG^spA	0	1153,1	1480,1		•	-
	58	HLAA 4142 1f20	CGCTTCCTCTGCGGGTACspC^spA	0	1098,1	•	1401,3	1441,4	-
5			CGCTTCCTGCGCGGGTACspC^spA	0	1098,1	-		1441,4	-
			CGCTTCCTCCACGGGTACspC^spA	0	1098,1	-		1441,4	-
			CGMTTCCTCCGCGGGTACspC^spA	0	1098,1	•	1401,3	1441,4	-
			CGCCTCCTCCGCGGGTACspC^spA	0	1098,1	-	1401,3	1441,4	-
			CACTTCCTCCGCGGGTACspC^spG	0	1114,1	-	-	1457,4	
	64	HLAA_4148_1f20	CGCTTMCTCCGCGGGTACspC^spG	0	1114,1	-	•	1457,4	-
			GTCCAAGAGCGCAGGTCTspT^spC	0	1206,2	-	-	-	1524,
			GTCCAAGAGCGCAGGTCCspT^spC	0	1191,2	-	-	1534,5	
10	87	HLAA_4533_1r20	GTCCAGGAGCTCAGGTCCspT^spC	0	1191,2	-		1534,5	1509,
	60	UI AA 5004 0-00	GGCCGYCTCCCACTTGTspGspC^spT	0	4400 4	 		 	4704
			GGCYGCCTCCCACTTGTspGspC*spT GGCYGCCTCCCACTTGCspGspC*spT	0	1463,4		4754.0	4704 7	1781,
			CGGAGTCTCCCACTTGCspGspC*spT	0	1448,4	-		1791,7	
	70	HI AA EO24 3-20	GGCCGCCTCCCACTTGCspGspC*spt GGCCGCCTCCCACTTGCspGspC*spC	-14	1448,4	-		1791,7	
	-	TLAA SUZA ZIZU	GGCCGCCTCCCACTTGCspGspC-spC	-14	1419,4	-			1737,
	72	HI AA 5271 1820	AGTGGGAGACTCCGCCCAspT^spG	0	1255,3	1582 6	1558,5		1573,
			CAAGTGGGAGGCGGYCCAspT*spG	ŏ			1558,5		1573,
			CAAGTGGGAGRCGGCCCAspT^spG	ŏ	1255,3		1558,5	-	1573,
15			CAAGTGGGAGGCGGCCCTspT^spG	ŏ	1246,3	-	1000,0		1564,
į			CAAGTGGGAGGCGGCCCGspT^spT	ō	1246,3	-		1589,6	-
•			CAAGTGGGAGGCGGCCCGspT^spC	ō	1231,3	-		1574,5	
:			CAAGTGGGAGGCGGCCMGspT^spG	0	1271,3	1598,6	_	-	1589,
			CAAGTGGGAGGCRGCCCGspT^spG	0	1271,3	1598,6	-	-	1589,
•			GCCCRTGAGGCGGAGCAspG^spC	0	1138,1	1465,4	-	1481,4	1456,
			GYCCATGCGGCGGAGCAspG^spC	0	1138,1	1465,4	-	1481,4	
			GCCCGTCGGGCGGAGCAspG^spC	0	1138,1	1465,4	-	1481,4	
20			GCCCATGTGGCGGAGCAspG^spC	0	1138,1	1465,4	-	1481,4	
			GTCCATGCGGCGGAGCAspG^spT	0	1153,1	-	-	1496,4	
	85	HLAA_5396_1f19	GCCCGTYGGGCGGAGCAspG^spT	0	1153,1	-	-	1496,4	
	86	HLAA_5397_1f19	GCCCATGAGGCGGAGCAspG^spT	0	1153,1		-	1496,4	1471,
			GCCCWTGTGGCGGAGCAspG^spT	0	1153,1		-	1496,4	
	88	nLAA_5399_1119	GCCMGTGTGGCGGAGCAspG^spT	0	1153,1		-	1496,4	1471,
	80	HI AA 5594 4-20	GCGGAGCCACTCCACGCAspC^spT	0	1113,1		1416,3		
			GCGGAGCCACTCCACGCAspC*spT	0	1113,1	-	1416,3		
06			GCGGAGCCACTCCACGCAspC^spA	ő	1122,1			1465,4	
25	92	HLAA 5594 1r20	GCGGAGCCCGTCCACTCAspC^spG	ö	1138,1			1465,4	1456,
	93	HLAA 5595 1r20	GCGGAGCCAGTCCACGCAspC^spG	Ö	1138,1	-	-	_	1456,
			GCGGAGCCMGTCCACGCAspC^spG	ŏ	1138,1			-	1456,
			GCGGAGCCACTCCACGCAspC^spC	Ö	1098,1	1425,4	-	1441,4	-
			GCGGAGCCCGTCCACGCAspC^spC	ō	1098,1	1425,4	-	1441,4	
		HLAA_5599_1r20	GCGGAGCCACTCCACGCAspG^spG	0	1178,1	-	-	-	1496,
	97	HLAA_5711_2f20	TGGAGGGCCKGTGCGTGspGspA^spG	0	1537,4	-	-	-	1855,
30	98	HLAA_5712_2f20	TGGAGGGYGAGTGCGTGspGspA^spG	0	1537,4	-	•	-	1855,
50	99	HLAA_5713_2f20	TGSAGGGCCGGTGCGTGspGspA^spG	0	1537,4	-	•	-	1855,
	100	HLAA_5714_2f20	TGGATGSCACGTGCGTGspGspA^spG	0	1537,4	-	•	-	1855,
	101	HLAA 5715 2f20	TGGAGGCACSTGCGTGspGspA^spG	0	1537,4	•	-	-	1855,
į	102	HLAA_5716_2f20	TGGAGGCACGTGMGTGspGspA^spC	0	1497,4	-	-		1815,
	103	HLAA_5717_2f20	TGGAGGCYGGTGCGTGspGspA^spC	0	1497,4	-	-	1840,7	1815,

TABLE V

	Mana	0		Primer	_			
No	Name HLAB 971 2f20	Sequence	CT	Masses	<u> </u>	С	G	T
1 2	HLAB_971_2f20 HLAB_972_2f20	CCCACTCCATGAGGCATspTspT^spC	10	1540,3	<u> </u>	1843,7	1883,8	1858,
-	TLAD 912 ZIZU	CCCACTYCATGAGGTATspTspT^spC	0	1540,3		1843,7	1883,8	1858,
3	HI AR 2064 1520	CGACGCCGCGAGTCMGAGspG^spA	00	44504				
4	HI AB 2062 1620	CGACGCCACGAGTCMGAGSpG^spA CGACGCCACGAGTCCGAGspG^spA	-28	1150,1	1477,4			1468,
5	HI AR 2063 1520	CGACGCCGCGAGTCCGAGSpG*SpA CGACGCCGCGAGTCCGAGSpA*SpG	-28	1150,1	1477,4	1453,3		1468,
6	HLAB 2064 1f20	CGACGCCRCGAGTCCRAGSpA*spG	0	1178,1	1505,4		1521,4	<u> </u>
۲	TIENE LOUY TIE	OCACCOCKCGAGTCCGAGSPA-SPG		1178,1	1505,4		1521,4	<u> </u>
7	HI AR 2221 1r19	GCCCTCCTGCTCCACCspC^spA	0	4000.2	1425,4	 	4444	
8	HI AB 2222 1r19	GCCCTCYTGCTCTATCspC^spA	10	1098,3			1441,4	
Ť	TILLIO_LALL_TTTO	COOCCIOTICOTOTATOSPO SPA	-	1098,3	1425,4		1441,4	-
9	HLAB 2591 2620	GGCCGGAGTATTGGGACspGspG^spG	0	1513,4			40567	
10	HLAB 2592 2f20	GGCCGGAGTATTGGGACspGspA^spG	0	1497,4	-		1856,7	
11	HLAB 2593 2f20	GGCCGGAGTATTGGGACspCspC^spG	-28	1405,4	-		1840,7	
12	HLAB 2594 2f20	GGCCGGAGTATTGGGATspCspG^spG	0	1488,4	1815,7		1748,7	-
13	HLAB 2595: 2f20	GGCCGGAGTTTTGGGACspCspG^spG	-28	1445,4	1772,7		1831,7 1788,7	
14	HLAB 2596 2f20	GGCCGGAGCATTGGGACspCspG^spG	-28	1445,4				
15	HLAB 2597 2f20	GGCCGGATATTGGGACspCspG^spG	-28	1445,4	1772,7		1788,7	
16	HLAB 2598 2f20	GGCCRGAATATTGGGACspCspG^spG	-28	1445,4			1788,7	-
17	HLAB 2599 2f20	GGCGGGMGTATTGGGACspCspG*spG	-28	1445,4	1772,7		1788,7	
	HLAB 25910 2f20	GGCCTTAGTATTGGGACspCspG^spG	-28	1445,4	1772,7		1788,7	
<u> </u>		этогине интесерносре вре	1-20	1443,4	1112,1		1788,7	 -
19	HLAB 2721 1f20	GGACSGGAGACACGGAAspC^spA	0	1122,1				1440,
20	HLAB_2722_1f20	GGACGRGGAGACACGGAAspC^spA	ō	1122,1				
21	HLAB 2723 1f20	GGACCGGAACACACAGAAspC^spT	0	1113,1	-		1456,4	1440,
22	HLAB 2724 1f20	GGACCGGAACACACAGACspC^spT	-14	1075,1		-	1436,4	1393,8
23	HLAB 2725 1f20	GGACCGGGAGACACAGAAspG^spT	0	1153,1	1480,4			1050,0
24	HLAB 2726 1f20	GGACCGGGAGATACAGATspC^spT	ō	1104,1	1431,4	1407,3	1447,4	1422,3
25	HLAB 2727 1f20	GGACCGGGASACACAGATspC^spT	ō	1104,1	1431,4	1407,3	1447,4	1422,3
26	HLAB_2728_1f20	GGACCGGGACACACAGATspC^spT	ō	1104,1	1431,4	1407,3	1447,4	1422,3
27	HLAB_2729_1f20	GGACCSGGAGACACAGATspC^spT	0	1104,1	1431,4	1407,3	1447,4	1422,3
					4,000,1	1100,50	,	
28	HLAB_2921_2f19	CAAGACCAACACAGspGspC^spT	0	1458,3	-		1801,6	
29	HLAB_2922_2f19	CAAGSCCCAGGCACAGspGspC^spT	0	1458,3	•	-	1801,6	-
30	HLAB_2923_2f19	CAAGACCAACACACGGspAspC^spT	-28	1414,3	-		1757,6	1732,5
31		GAAGGCCTCCGCGCAGspAspC^spT	-28	1414,3	-	-	1757,6	1732,5
32		CAAGGCCMAGGCACAGspAspC^spT	-28	1414,3	-	•	1757,6	1732,5
33		CAAGSGCCAGGCACAGspAspC^spT	-28	1414,3	•	-	1757,6	1732,5
34	HLAB_2927_2f19	GAAGACCAACACACAGspAspC^spT	-28	1414,3	-	-	1757,6	1732,5
35	HLAB_3021_2f19	GCACAGACTGACCGAGspTspG^spG	0	1528,4	•	-	1871,7	-
36	HLAB_30211_2f19	ACACAGACTTACAGAGspAspG^spA	-28		1820,8	-	1836,8	•
37		ACACAGACTTACCGAGspAspG^spG ·	0	1537,4	1864,7	<u> </u>	- 1	
38	HLAB_3023_2f19	RCACAGACTGACCGAGspAspG^spG	0	1537,4	1864,7	•	-	_
39	HLAB 3024 2f19	GCACAGACTGGCCGAGspTspG^spA	-28	1481,4	1811,7	<u> </u>	1827,7	
40	TLAB_3025_2119	ACACAGACTTACCGAGspTspG^spA	-28	1481,4	1811,7		1827,7	
41	HIAD 2025 2119	RCACAGACTGACCGAGspTspG^spA	-28	1481,4	1811,7	-	1827,7	
42	HIAD SOOF ONE	ACACAGGCTGACCGAGSpAspG^spA	-28	1493,5	1820,8		1836,8	
43 44	HI AD 2000 0440	RCACAGACTGACCGAGspAspG^spA	-28		1820,8		1836,8	<u> </u>
	HIAD SUZU ZITU	GCRCAGACTTACCGAGspAspG^spA	-28	1493,5	1820,8		1836,8	· •
┟╩┨	TILAD SUZIU ZITS	ACACRGACTTACCGAGspAspG^spA	-28	1493,5	1820,8		1836,8	
46	HI AR 2024 2520	CGCGTCTCACACCCTCC~~A~~CA~~A	20	4440.4			4555	
47	HI AR 3622 2620	CGGGTCTCACACCCTCCspAspC^spA CGGGTCTCACAYCATCCspAspG^spA	-28	1413,4	47047		1756,7	
48	HI AR 2022 2020	CCCVTCTCACACCCTCCACA	-14	1467,4	1794,7	1770,6	1810,7	1785,6
49	HI AD 2024 2420	CGGKTCTCACACCCTCCspAspG^spA	-14	1467,4	1794,7	1770,6	1810,7	1785,6
50	HI AR 362E 2020	CGGGTCTCACACTTGGCspAspG^spA	-14	1467,4	1794,7	1770,6	1810,7	1785,6
51	HI AR SESE SES	CGGGTCTCACACCCTCCCCACACCCTCCCCACACCCTCCCCACACCCTCCCACACCCTCCCCACACCCTCCCACACCCTCCCACACCCTCCCACACCCTCCCACACCCTCCCCACACCCTCCCCACACCCTCCCCACACCCTCCCCACACCCTCCACACCAC	-14	1483,4				1801,6
-	11LAD_2020_2120	CGGGTCTCACACCCTCCspAspG^spT	0	1472,4			1815,7	:_
52	HI AR 3624 4-00	CCCACCTCCCACCCCTACAAT	00	400= :		 _		4465.5
53	HI AR 3632 4-20	CCCASGTCGCAGCCGTACspA^spT CCCABGTCGCAGCCATACspA^spT	-28	1085,1		1388,3	1428,4	1403,3
54	HLAB 3632 4-20	CCCASGTCGCAGCCATACspA*spT	-28	1085,1		1388,3	1428,4	1403,3
		UUUNGUTUGUNGUUAAAUSPA~SPI	-28	1085,1		1388,3	1428,4	1403,3

	55		CCCACGTCGCAGCCAGACspA^spT	-28	1085,1	-	1388,3		140:
	56		CCCACGTCGCAGCCGCACspA^spT	-28	1085,1	-	1388,3	1428,4	140:
	57		CCCACGTCGCAGCCTTACspA^spT	-28	1085,1	-	1388,3	1428,4	1403
	58	HLAB_3637_1r20	CCCACGTCGCAGCCGTACspG^spT	0	1129,1	•	1432,3	1472,4	1447
				1					
	59		TCCGGCCCCAKGTCGCAGspC^spC	0	1114,1	1441,4	-	1457,4	1432
	60	HLAB_3692_1f20	TCGGGCCCCASGTCGCAGspC^spC	0	1114,1	1441,4	-	1457,4	1432
	55	HLAB_4121_2f20	GGCGCCTCCTCCGCGGGspTspA^spC	-28	1444,4	9	1747,6	-	-
	56		GGCGCCTCCTCCSCGGGspCspA^spT	. 0	1472,4	1799,7	-	1815,7	-
_	57	HLAB 4123 2f20	GGCGCYTCCTCCGCGGGspCspA^spT	0	1472,4	1799,7	-	1815,7	=
5	58		GGCGTCTCCTCCGCGGTspTspA^spT	0	1462,4	-	1765,6	-	-
	59	HLAB_4125_2f20	GGCGCCTCCTCCGCGGGspTspA^spT	-14	1473,4	-	1776,6	-	•
	60	HLAB_4181_2f20	TCCTCCGCGGGTATGAAspCspA^spG	0	1481,4	1808,7	-	-	-
	61	HLAB_4182_2f20	TCCTCCACGGGTACCACspCspA^spG	0	1457,4	-	-	**	1775
	62	HLAB_4183_2f20	TCCTGCGCGGGTACCACspCspA^spG	0	1457,4	-	-	-	1775
	63	HLAB_4184_2f20	TCCTCCGCGGGTACCACspCspA^spG	0	1457,4	-	-	-	1775
	64		TCCTCTGCGGGTACCACspCspA^spG	0	1457,4	-	-	-	1775
	65		TCCTCCGCGGGTACCAGspCspA^spG	0	1497,4	1824,7	1800,6	1840,7	1815
10	66	HLAB_4187_2f20	TMCTCCGCGGGTACCGGspCspA^spG	0	1497,4	1824,7	1800,6	1840,7	1815
10	67		TCCTCCGCGGGTACCAGspCspG^spG	0	1513,4	-	-	1856,7	-
		7							
	68	HLAB 4191 2r20	AATCCTTGCCGTCGTAGspGspC^spT	-14	1474,4	1801,7	-		-
	69		AATCCTTGCCGTCGTAGspGspC^spA	-28	1469,4		•	1812,7	
	70	HLAB 4193 2r20	AATTCTTGCCGTCGTAGspGspC^spG	0	1513,4	1840,7		1856,7	1831
	71		AATCTTTGCCGTCGTAGspGspC^spG	0	1513,4	1840,7	-	1856,7	1831
	72		AATCCTTGCCGTCGYAGspGspC^spG	0	1513,4	1840,7	-	1856,7	1831
				<u> </u>				3000,0	
	73	HLAB 4351n 1r20	TCMTTCAGGGCGATGTAAspT^spC	-14	1201,3	-	1504,4		1519
15	74	HLAB_4352n_1r20	TCGTTCAGGGCGATGTAAspT^spT	0	1230,3	-	1533,5		-
7.0									
	75	HLAB_5271_1f20	CAAGTGGGAGGCGGCCCTspT^spG	0	1246,3	-		-	1564
	76	HLAB_5272_1f20	CAAGTKGGAGGCGGCCCGspT^spG	0	1271,3	1598,6	1574,3	-	1589
	77	HLAB_5391_1f20	GGCCCGTGYGGCGGAGCAspG^spC	0	1138,1	*	•	1481,3	1456
	78		GGCCCGTGTCGCGGAGCAspG^spG	0	1178,1	1505,4	-	-	-
	79		GGCCCGTGWGGCGGAGCAspG^spG	0	1178,1	1505,4	-		-
	80	HLAB_5394_1f20	GGCCCGTGAGGCGGAGCAspG^spT	0	1153,1	-	· -	1496,4	-
20									
20	81	HLAB_5591_1r20	GCGGAGCGACTCCACGCAspC^spT	0	1113,1	-	-	1456,4	-
	82	HLAB_5592_1r20	GCGGAGCCACTCCACGCAspC^spT	0	1113,1			1456,4	-
	83	HLAB_5593_1r20	GCGGAGCCAATCCACGCAspC^spT	0	1113,1	•	•	1456,4	-
	84	HLAB_5594_1r20	GCGGAGCCACTCCACGCAspC^spG	0	1152,1	-	-		1470
	85	HLAB_5595_1r20	GCGGAGCGACTCCRCGCAspC^spA	-14	1122,1	1449,1	1425.3	-	-
	86	HLAB_5596_1r20	GCGGAGCSACTCCACGCAspC^spA	-14	1122,1	1449,1	1425,3	-	
	87	HLAB_5597_1r20	GCGGAGCCCGTCCACGCAspC^spA	-14	1122,1	1449,1	1425,3	-	-
									
	88	HLAB_5711_1r20	CTCCAGGTAYCTGCGGAGspC^spG	0	1154,1	1481,4	-	-	_
25	89	HLAB_5712_1r20	CTCCAGGTRTCTGCGGAGspC^spC	0	1114,1	1441,4	1417,3	-	_
			•						
	90	HLAB_583_1r19	ACCTGGAGAACGGGAAGspG^spA	0	1178,1	1505,4	-	1521,4	



TABLE VI

					ستداد المساديدي				
·					Masses				
	No		Sequence	CT		Α	С	G	T
	1		CATTGAAGAAATGACACTspC^spC	0	1098,1	-	1392,3	-	-
	2	DRB1_1252_1r20		0	1230,1	-	-		1548,
	3		CATTGAAGAAATGACATTspC^spA	0	1113,1	1440,4	1416,3	1456,4	1431,
	4	DRB1_1254_1r20		0	1113,2	1440,4	1416,3		1431,
	5	DRB1_1255_1r20	CRTTGAAGAAATGACACTspC^spA	. 0	1113,3	1440,4	1416,3	1456,4	1431,
	-	DDD4 4004 4440	CATOTATALOGALOAGO	1					
5	6 7		CATCTATAACCAAGAGGspA^spA	0	1162,1	4505			1480,
	8		CTTCTATCACCAAGARGspA^spG CTTCTATAATCARGAGGspA^spG	0	1178,1	1505,4			1496,
	9		CGTCCATAACCAAGAGGspA*spG	0	1178,1	1505,4			1496,
	10		CATCTATAACCAAGAGGspA*spG	0	1178,1	1505,4			1496,
	11		CTTCCATAACCRGGAGGspA*spG	0	1178,1	1505,4			1496,
	12		CTTCGATAACCAGGAGGspA*spG	0	1178,1	1505,4			1496,
	13		CTTCTATAACCTGGAGGspA^spG	0	1178,1	1505,4	-	-	1496,
	-	·	OTTOTALACOT GGAGGSPA'SPG	╁╩	1178,1	1505,4	-	· -	1496,
10	14	DRB1_1971_1r20	CGTCGCTGTCGAAGCGCAspG^spG	0	1178,1	1505,4			4400
	15		CGTCGCTGTCGTAGCGCGspC^spG	0	1154,1	1000,4		-	1496,:
	16		CGTCGCTGTCGAAGCGCAspA^spG	ő	1162,1	<u> </u>			1472,
	17		CGTCGCTGTCGAAGYGCAspC^spG	-28	1110,1	1437,4		1453,4	1480,: 1428,:
	18		CGTCGCTGTCGAASCGCAspC^spG	-28	1110,1	1437,4	-	1453,4	1428,
				120	1110,1	1401,4		1400,4	1420,
	19	DRB1_2271_1f20	CGACAGCGACGTGGGGGAspC^spT	0	1113,1	1440,4	-		
	20	DRB1_2272_1f20	CGACAGCGACGTGVGGGAspG^spT	0	1153,1	1480,4			1471,
15						11.00,1			147.5
13	21	DRB1_2611_1r20	TTCTGGCTGTTCCAGTACspT^spG	0	1231,2	_	-	1574,5	-
	22		TTCTGGCTGTTCCAGTACspC^spC	0	1074,1	-	1377,3	-	
	23	DRB1_2613_1r20	TTCTGGCTGTTCCAGTAGspT^spC	0	1231,2	-	1534,4	_	-
	24	DRB1_2614_1r20	TTCTGGCTGTTCCAGTRCspT^spC	-14	1177,2	1504,5	1480,4	1520,5	-
	25	DRB1_2615_1r20	TTCYGGCTGTTCCAGGACspT^spC	-14	1177,2	1504,5	1480,4	1520,5	-
• (
	26		CTGGAACAGCCAGAAGAspA^spC	-28	1122,1	1449,4	• -	-	_
	27	DRB1_2862_1f19	CTGGAACAGCCRGAAGGspA^spC	0	1138,1	1465,4	1441,3	-	1456,3
20	Ш								
	28		GAAGGACHTCCTGGAGCAspG^spG	0	1178,1	•	1481,3		
	29		GAAGGACATCCTGGGAGAspC^spA	-14	1108,1	1435,1	•	1451,4	
	30	DRB1_2993_1f20	GAAGGACATCCTGGARGAspC^spA	-14	1108,1	1435,1	•	1452,4	
	31		GAAGGACYTCCTGGAAGAspC^spA	-14	1108,1	1435,1	-	1453,4	
	32	DRB1_2995_1f20	GAAGGACATCCTGGAGCAspG^spA	0	1162,1	1489,4	-	1505,4	•
	33		GAAGGACHTCCTGGAGCGspG^spA	0	1178,1	-		1521,4	
i	34	DRB1_2997_1f20	GAAGGACHTCCTGGAAGAspC^spG	0	1138,1	1465,4	-		
25	25	DDD4 2004 4-00	070700447400707004						
	35	DBR1_3081_1/20	GTCTGCAATAGGTGTCCAspC^spG	0	1138,1	-	1441,3		
	36	DRB1_3082_1F20	GTCTGCARTAGGCGTCCAspC^spC	-14	1084,1	1411,4	1387,3	1427,4	1402,3
	37	DRB1_3083_1720	GTCTGCAGTAATTGTCCAspC^spC	-14	1084,1	1411,4	1387,3	1427,4	1402,3
	38 39		GTCTGCACACGGTGTCCAspC^spC	-14	1084,1	1411,4	1387,3	1427,4	1402,3
	39 40		GTCTGCAGTAGGTGTCCAspC^spC	-14	1084,1	1411,4	1387,3	1427,4	1402,3
	70	PVB 1 2000 11X0	GTCTGCAATAGGTGTCCAspC^spC	-14	1084,1	1411,4	1387,3	1427,4	1402,3
	41	DPR1 344 4640	TGCACACACAACTAGGG		4401.1				
		DRB1_341_1f19	TGCAGACACAACTACSGspG^spG	0	1194,1		1497,3		1512,3
30	42	DRR1 3454 4-20	CCCTCCACTCTCAATOTO TA C	┝┯┦	4404.5	4840 =	445 : -		
		DRR1 3452 4-20	CGCTGCACTGTGAATCTCspT^spC CTCTGCACTGTGAAGCTCspT^spC	0	1191,3	1518,5	1494,4		-
	44	DRB1 3453 1r20	CGCTGCACTGTGAAGCTCspT^spC CGCTGCACYGTGAAGCTCspT^spC	0	1191,3	1518,5	1494,4		
			OCCIONOTO TO MIGGIOSPITSPO	. 0	1191,3	1518,5	1494,4		

The resolution achievable by 19 markers each for HLA-A and HLA-B and the ten markers for HLA-DRB1 are listed in Tables VII to IX below.

TABLE VII

Frequent Alleles of HLA-A	Group of frequent Alleles with same four- digit type	Rare Alleles with same Mini- Haplotype Profile	Resolution (in %)
A*0101	A*010102	A*0103, 2000, A*0109	98,3
A*0201	A*020103, A*020104, A*020109	A*0204, A*0225, A*0231, A*0232N, A*0242, A*0260, A*0253N, A*0258, A*0260, A*0264, A*0267	93,4
	A*020102		100
	A*020105		100
	A*020106		100
	A*020107		100
A*0301	4 (050) (010) 3 (40) (010) (02)	A*0303N, A*0304, A*0305, A*0306, A*0311N	97,6
	A*030102		100
	A*030103		100
A*2301	A PSO	A*2306, A*2308N	98,6
A*2402	A*240202, A*240202, A*240204	A*2404, A*2427, A*2432, A*2426, A*2427, A*2432, A*2435, A*2436N, A*2437, A*2439	94,5
A*2902	A*290201	A*2906, A*2908N	98,3
	A*290202		100
A*3001	A*3001		100
A*3002	A*3002		100

Capture: Alleles in a same field have the same mini-haplotype profile; grey high lighted are all alleles with identical sequences over exons 2 and 3.

TABLE VIII

Frequent Alleles of HLA-B	Groups of frequent Alleles with same four-digit type	Rare Alleles with same Mini- Haplotype Profile	Resolution (in %)
B*0702	B*070201, B*070202, B*070203, B*070204	B*0703, B*0721, B*0722, B*0723, B*0730, B*0733, B*0735	98,0
B*0801	BX0801	B*0808N, B*0818, BEESTEN	99,3
B*1302	B*1302	B*1308	99,6
B*1501	B*150103, B*150104	B*1528, B*1533, B*1534, B*1560, B*1575, B*1578, B*1579N, B*1581, B*1582	97,6
	B*150102		100
B*1801	B*180102	B*1805, E. 18 1/1	99,3
B*3501	B*350102	B*3507, B*3541, B*3541, B*3542, B*5305	98,7
B*3503	B*3503	B*3536	99,6
B*4001		B*4011, B*401401, B*401402, B*401403, B*4022N	98,7
	B*400103		100
	B*400104	B*4004	99,6
B*4402	B*440203	B*4411, B*4422, B*4423N, B*4433, B*4434, B*4435	97,8
B*4403	B*440301	B*4413, B*4426, B*4429, B*4430, B*4432, B*4436, B*4437, B*4438, B*4439	98,2
74-10-	B*440302	B*4407	99,6
B*5101	B*510102,	B*5118, B*5126, B*5127N, B*5128, B*5126, B*5127N, B*5128, B*5133	97,6
•	B*510103	•	100
7.4.	B*510104	B*5124	99,6
B*5701	B*570101	B*5706, B*5708	99,5
	B*570102		100

Capture: Alleles in a same field have the same mini-haplotype profile; grey high lighted are all alleles with identical sequences over exons 2 and 3.



TABLE IX

Frequent Alleles of HLA-DRB1*	Groups of frequent Alleles with same four-digit type	Rare Alleles with same Mini- Haplotype Profile	Resolution (in %)
DRB1*0101	DRB1*010101	DRB1*0105, DRB1*0107, DRB1*0111	98,9
	DRB1*010102		100
DRB1*0301	DRB1*030101, DRB1*030102	DRB1*0307, DRB1*0312, DRB1*0313, DRB1*0315, DRB1*0316, DRB1*0318, DRB1*0322, DRB1*0323	97,2
DRB1*0401	DRB1*040101, DRB1*040102	DRB1*0409, DRB1*0426, DRB1*0433	98,6
DRB1*0701	DRB1*070101, DRB1*070102	DRB1*0703, DRB1*0704, DRB1*0705, DRB1*0707	98,3
DRB1*1101	DREASH (0.40), DRB1*110103, DRB1*110104, DRB1*110105	DRB1*112701, DRB1*112702, DRB1*1130, DRB1*1139	97,5
DRB1*1104	Dienstein (220m), Dienstein (2000)	DRB1*1134, DRB1*1146	98,9
DRB1*1302	DRB1*130201, DRB1*130202	DRB1*1331, DRB1*1339, DRB1*1341	98,6
DRB1*1501	DRB1*150101, DRB1*150103, DRB1*150105	DRB1*1503, DRB1*1506, DRB1*1509, DRB1*1513	98,0
	DRB1*150102		100
	DRB1*150104	DRB1*1512	99,4

Capture: Alleles in a same field have the same mini-haplotype profile; grey high lighted are all alleles with identical sequences over exon 2 (base 101 to 356)

The complete list of HLA alleles and sub-groups generated by the most informative mini-haplotyping markers (ten each for HLA-A, HLA-B and HLA-DRB1) are listed in Tables X to XII below.



TABLE X

		INDEC X
	Position cDNA Arabas	95 96 97 (80 411 412 412 514) 536 637 638 (537 638 637 638 637 638 637 638 638 637 (538 638 637 638 638 637 638 638 637 638 638 637 638 638 638 638 638 638 638 638 638 638
	A*6806	
	A*0244	TCTACCACAGCCA AGG AGG TG TAGG G G A C TAGG G T C CAG G T
	A*0254	TCTACCA A G C C C A G G G A C T G G G G A C T G G G T C C G G T
	A'0205	TCTACCA A G T C C A A G G A G T G T G G G G A C T G G T C C G T
	A*0208	T C T C C A G G A G A G A G A G A G A G A G A
	A*6815	TCTCCAAAAGTCCAAGGAAGTTGTGGGAACT
	A*6802 A*6818N	TCTECCARAGTECCARGGAGET GT GT AACT GG CC GT
5	A*0228	TCTCCAMAGTCCAMGGAGTGTGGGGACTCGGTCGGT.
	A*0206 A*0214	TCTACCAAAAGTACCAAAGGAAGATGTAAAGACTAAAAAAAA
	A*0221 A*0257 A*0251	TCTTCCAAGAGTCCAAGGGAGGTGTTGTTGCGGGACTGGTCCGGGT
	A'0261	TC TO C C A SIA C TO C C C C C C C C C C C C C C C C C
	A*0210	TCTCCAAAATACCAAGGAAGTTGTTTTTTTTTTTTTTTT
	A'6901	TCT CCA A G T CCA G G A G T G T G G G A A C T G G C C G T ,
	A*2504 A*2608	TCTCCCARAGCACATGTGTGGGAACTCGGCCGGT
	A*2803	T C T II C C A III A C T II C C A III C C A II
10	A*2608	TCTCCAAAGTCCAAGGAGATGTGTGGGAACTGGGCCGT
	A*2610 A*2609 A*250101	TCTTCCCAAAAGTCCCAAGGAAGTTGTAAGGAACTTGTGGAAACTTGTCTCCCAAGAAGTTGTGTAAGGAACTTGTCTCCCAAGAAGTTGTAAGGAACTTGTGGAAACTTGTGAAGAACTTGTGAAAACTTGTGAAAACTTGTGAAAACTTGTGAAAAACTTGTGAAAAACTTGTGAAAAAAAA
	A*250102 A*2601	TCTMCCCAMA 9 TMCCCAMCCAACMITCTMA 9 9 AAAC TMA 0 9 CCMG T (
	A*2602 A*2603	IT C TROIC C A REM A G TROIC C A REM G G A G SEET G T SHEETEN C C TROIC C TROIC C TROIC C C A REM G G A G SEET G T SHEETEN C C TROIC C
	A*2611N A*2614 A*2618	TCTTCCAAAACAAAACAAAACAAAACAAAACAAAACAA
	A*2617 A*2604	TO THE C C AND A G THE C C AND C C A C C C C C C C C C C C C C C C C
	A'6603 A'2612	TCTBCCAAAGTCCAAGGAGGAGGTGTTGTTGGGAAACTTGGGGCCGGT, C
15	A*2618 A*4301	
:	A*260701	
	A*280702	TCTCCA AGAGAT GTAGGGCC GTG
. ;	A*2619	TCTECCA AGT CCA GGAG TG TG AGGACT GGGCC GTC
	A*2401 A*3405	TCTACCAAAAGTACCAAAAGAAAGTAGTAGTAGGAAACTAAAGTAGTAGTAGTAGTAGTAGTAGTAGTAGTAGTAGTA
	A*6602 A*2502	TCTCCCAAAGTCCAAGGTGTGTGGGAACTGGGGCGGTG
	A*2613 A*6601	T C T A C C A A A G T B C C A C G A G A T G T A G G A A C T B G G C C G G T G T G T G T G T G T G T G
~^	A*5504 A*0241	TOTAL C A A G T G C A G G A G T G T G G A A C T G G G C C G G T G
20	A*106	
	A*1103 A*1104	
	A*1107 A*110101	TOTAL COMMAN COMMON AND COACHE TO TEST A GOLAC TEST COMMON TO
	A*110102 A*1102	
	A*1109 A*1112	1
	A*1115 A*1113 A*1105	TT TT A C C C C C A A C C C C C A A C C C C
	A'1114	TCTTCCCGAACCCAACGGAGTTGTAAACTTGTAACTTCTTCCCGAACCCAACGGAACTTGTCTTCCCGAACCCAACGGAACTTGTAACGAACTTGGACCCAACGGAACTTGTAACGAACTTGGACCAACGGACTGGACTTGTAACGAACTTGGACCAACGAACTTGAACGAAC
25	A*1110 A*680 3	T C T C C C C C C C C C C C C C C C C C
	A*1111	TCTCCCGAGGAGGTGTGCACTGGGCCGGTG
	A*1108	
	A*6805 A*6820	T C T C C G G A G T C C A G G G A G T T G T G G A C T G G G C C G T G T G T G T G G G A G T G G G A G T G G G A A C T G G G C C G T G T G G G A A C T G G G C C G T G T G G G A A C T G G G C C G T G T G G G A A C T G G G C C G G T G T G G G A A C T G G G C C G G T G T G G G A A C T G G G C C G G T G T G G G A A C T G G G C C G G T G T G G G A A C T G G G C C G G T G T G G G A A C T G G G C C G G T G T G G G A A C T G G G A A C T G G G C C G G T G T G G G A A C T G G G A A C T G G G C C G G T G T G G G A A C T G G G A G T G G G A G G T G G T G G G A G T G G G A G T G G G A G T G G G A G T G G G A G T G G G A G G T G G T G G G A G T G G G A G G T G G T G G G A G G T G G T G G G A G G T G G T G G G A G G T G G T G G T G G G A G G T G G T G G T G G G A G G T G G T G G T G G T G G T G G T G G T G G T G G T G G T G G T G G T G G G A G G T G T G G T G T G G T
	A*680301 A*680302	TCTCCCGGACCCACGGACGTGTGTGGGAACTTGGGGAACTTGGGTG
	A*6804	TCT CCG AGT CCA GGAGT GT GGAAT TO GGCC GT GT G
	A*680101 A*680102	
30	A*680103 A*6807	TC THE C C G G A G TT G C C A G G G A G G T G G T A A C T G G G A A C C T G G G T G G T C C C G G G A G G T G G G A A C C T G G G A C C C G G G A C C C G G G A C C C G G G A C C C G G G A C C C G G G A C C C C
	A*6811N A*6812 A*6817	TTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTT
	A*6819 A*6821	T C T T T T C C C C C C C C C C C C C C
	A'6523	TO THE COURSE A AGE TO GO GO A AGE TO GO
	A'6824 A'6816	CCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCC
	A'6813	TC TEC C GET A G TEC C A G G G A G T T G T T G G G A A C T G G G G G G T G T G T G T G G G G G

5	A*6810 A*6814 A*6808 A*0312 A*3402 A*3403 A*3404 A*3102 A*3107 A*3107 A*3106 A*31062 A*3109 A*33001 A*	T C T T C T T C T T C T T C T T C T T C T T C A A T C C A A T T C C A A T T C C A A T T C C A A T T C C A A T C C A A T C C A A T C C A A T C C A A T C C A A T C C A A T C C A A T C C A A T C C C C			AA AA AA AA AAAAAAA AA	TO T TT T TT T T TT TTTTTT C						A	- T T T T T T T T T T T T T T T T T T T	66666		AA G A GG G AA, A AA GGGGGGG T	0 00 00 00 00 00 00 00 00 00 00 00 00 0	1"	C C C C C T TT TTTTTT C	TITITION TO THE TITITION TO TH				0 0 00 00 00 00 00 00 00 00 00 00 00 00		6 6 6 6 6 6 6 6 6 6 6 6 6 6 6 6 6 6 6 6	1
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	A*3005 A*3012 A*3003		G .		A G A G	T	00 0	C	***	000		A G	T T	G G	TTTT	A A A	G G	A	c c	T T T	6 6 6	6	C	0000	000	3 T	
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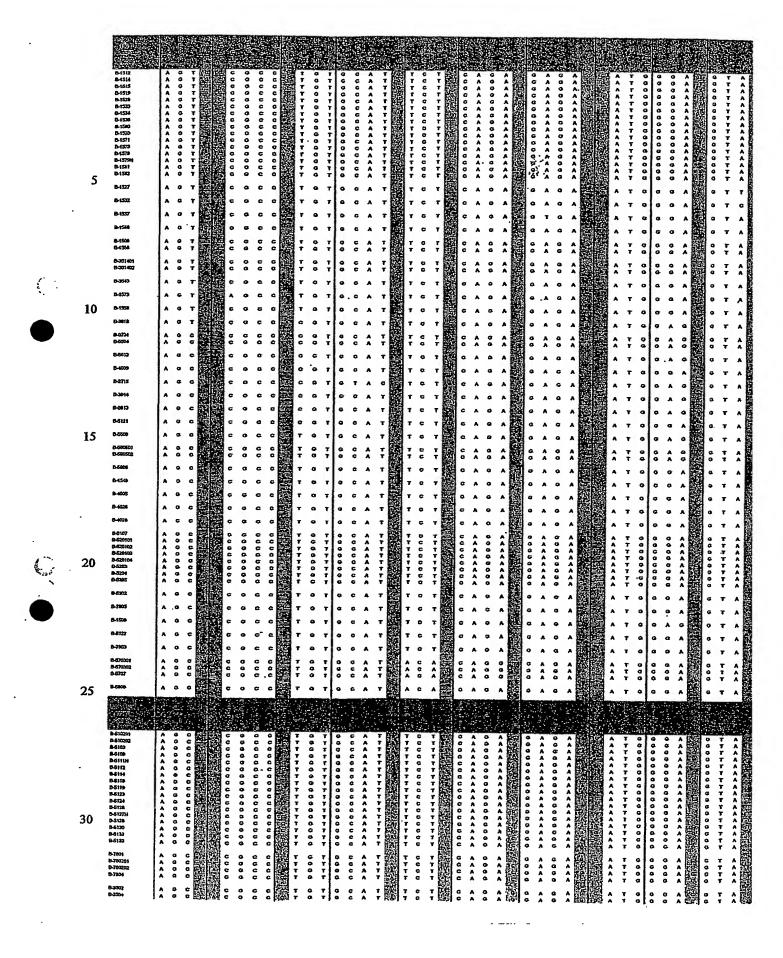
10	A*2307N A*2308N A*2308N A*2308 A*2310 A*2413 A*2300 A*2413 A*2300 A*2418 A*2418 A*2418 A*2418 A*2416 A*3207 A*0102 A*2417 A*0252 A*0213 A*02217 A*0213 A*02217 A*0222 A*0243 A*0228 A*0245 A*0248	TOUR CONTROL OF THE C	CCCCCCC C C C C C C C C C C C C C C C	GOGG G G G G G G G G G G G G G G G G G	ARRARA A AA AA AA AA AA AAAAA AA AA AA A	CCC C CC C C C C C C C C C C C C C C C		A A G G G A A A C C C C C C C C C C C C		CCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCC
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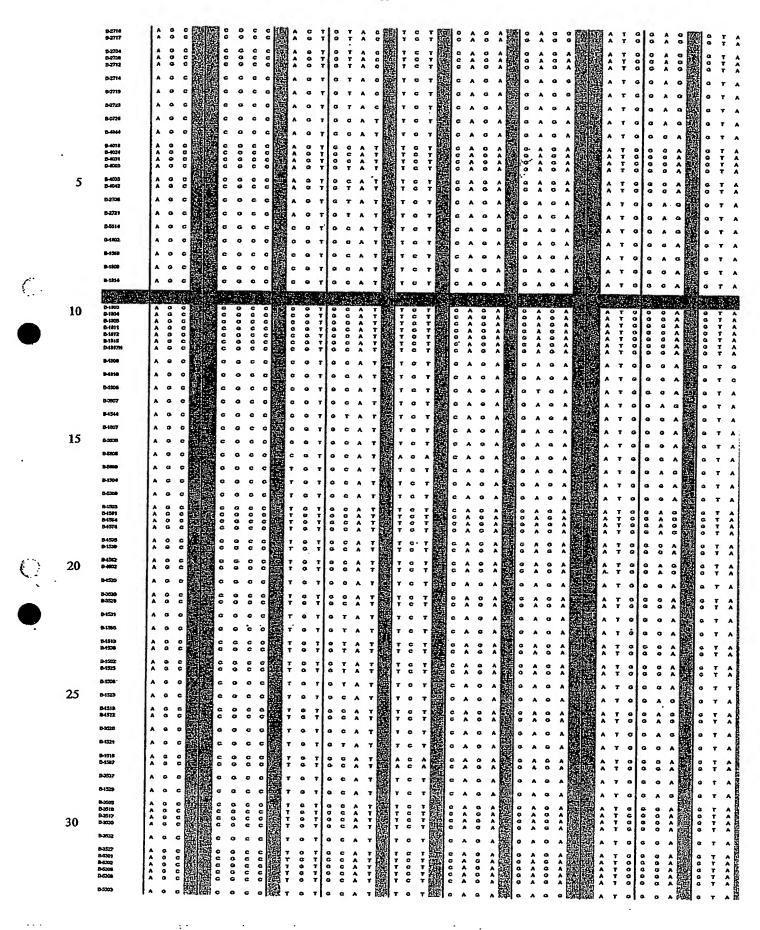
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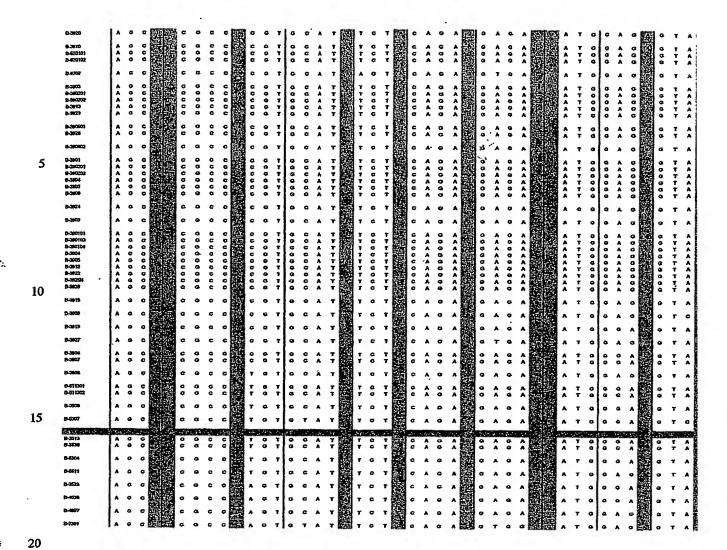


TABLE XII

	Position in cDNA	125	126	127	128	193	194	195	100	Ton	198	199	200	224	225	226	922	261	262	263	264	283	284	285	286	96 2	97 29	a P290	201	309	310	311	338	339	340	3331	342	343	344
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	DRB1-0706		т	A	A	G	A	G			c	G	7	A	G	т			G	A	G	G	A	c			C A			G	G		G	G	G		T T	G	G
	DRB1-0708		т	A	A	G	A	G			c	G	т	A	G	T			G	A	G	G	A	c		A (C A			в	Ģ	т	G	G	G			G	G
	DRB1-0441		T	G	A	G	A	G			C	G	7	A	G	T			G	A	G	G	A	C		A (з А		Š	G	G	T	G	G	G		τ	G	T
	DRB1-0439 DRB1-0416		T	G	A	G	A	G			c	G		A	C	T			G	Α.	G	G	A	C		A (-			G	G	7	G	G	6			G	TOTAL
_	DRB1-0402		-	G	A	6	A	G			c	G	-	A	G	T		è	G	A	G	G.	A	C			B A			G	G G		G	G	G			G G	G
5	DRB1-0412 DRB1-0418		T	G	A	G	A	G			C	G	7	A	G	Ţ			9.6	A	0	G	A	CC		A (C A		· 连	G	G	-	G	G	G		т	G	Т
	DRB1-0414		T	G	A	G	A	G			c		+	A	G	T			G	A	G		A	c			C A			G	G G	7	G	G	G			G G	G
	DRB1-0438		T	G	A	в	A	в			c	G	7	A	G	T			G	A	G	G	A	c		A ¢	3 A			G	в	7	G	G	a		T	G	G
	DRB1-0413		T	G	A	G	A	9			C	G	7	A	G	T			в	A	G	G	A	C		A C	3 A			G	G	7	G	G	6		T	G	T
	DRB1-0422		T ESTA	G	A	G	A	G			C Bage	G PSS	T	A	G	T		ľ	G	A	G K295	G	A	C		A (3 A			G	G	T	G	G	G		T	G	T
	DRB1-0409		T	G	A	G	A	G			C	G	-	A	G	T			G	A	G	G	AA	C		A				G	G		G	G	G		T	G	G
10	DRB1-0426 DRB1-0433		T	G	A	6	A	G			C.	G	Ŧ	A A	G	T			G	A	Ĝ	G	Å.	CC		A	3 A			G	G	귀	G	G	GG		٠T	G	00
	ORB1-0437		T	G	A	G	A	9			C		T	۸	3	T			G	A	G	G	A	C		A (G		7	G		G			G	T
	ORB1-040301 ORB1-0411		T	G	A	G	A	G			C	G	Ŧ	A	G	Ŧ			G	A	Ĝ		A	CC		A G				G	G	7	G		6			G	T
	DRB1-0427 DRB1-040701		T	G	A	G	A	G			c	-	T	A	G	T T			G	A	G	G	A	C		A 6				G			G.		9		Ť		T
	DRB1-040702 DRB1-040703		T	G	A	G	A	G			C	G	Ŧ	A	G	T			G	A	G	G	A	CC		AC	A			6	G	T	G G	G	000		T	G	GGG
	DRB1-0417 DRB1-0404		T	G	A	G	A	G			C	G	7	A	G G	T			G	A	G	G	A	C		A G				G		1	G G		G				G T
	DRB1-0410 DRB1-0423 DRB1-0432		TTT	6	AAA	600	AAA	6			000		Ŧ	AAA	6	T T			000	A	G G	G	A	000		A G	A E			G	G	Ŧ	G	G	G		Ŧ	G	TB
15	DRB1-0440 DRB1-0444		Ť	G	A	G	A	G			CC	G	ŧ	Â	Ğ	Ť			G	AAA	G	G	Α	000		A 6 A 6	3 A			G	G	7	6	G	000	14	Т (G	TTT
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	DRB1-040503 DRB1-040504 DRB1-0408		T	6	AAA	000	A A A	000			000	G	7	A	G	TTT		Ü	G	A	G	G	A	C		A G	A			G	G	7	G	G	G	N	T	G	G
	DRB1-0429 DRB1-0430		T	G	A	G	A	G			C	G	Ŧ	A A	G	T			6	A A	6	G	Α	000	A	A 6 A 6	A			G	G	T		G	990		T (G	S 0 0
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20	DRB1-0424 DRB1-0425		T T	G	Â	G	A	G					7	A	G	T			G	A				C		3 G A C				-		- 1			G	3			9
20	DRB1-0438		T	G	A	G	A	G					-	A	G	T			G	٨	6			C		A C	•			_	_	- 1			G	譜		_	7
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	DRB1-0415 DRB1-040302		T	G	<u>^</u>	G	A	0			C	G	1	A	G	T			9	A	G	G	A	C		A 0	. A			Ģ	G	T	G	G (G		т (3 .	
•	DRB1-0435		T	G	À	G	A	G			c	G	-1	A	G	7			G	A	G	e.	A	C		\ G	A			G	G G	-	G G	G ,	3		T (3 ' 3 (NAME OF TAXABLE PARTY.
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	DRB1-0428 DRB1-0443		Ŧ	G	A	G	A	G					Ŧ	A	G	Ŧ			G	A				CC											00		T (3 43
25	DRB1-1122		T	G	A	G	A	G			c	G	٦	A	G	T			G	A	0	G .	A	c		. с	A			G		1	G		G	3	т с		H
	DRB1-0406 DRB1-0446			G	1	G	A	G					Ŧ		G G	Ŧ			G		G			CC		G									GG		T		
	DRB1-0420		T	G	A	G	A	G			c	G	7	A	G	T			G	A	G	G.	A	C		, G	A			G	G .	٠.	G	G	G		т с	3 (
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	DRB1-1326 DRB1-1427		T	G	Â	G	A	G			c	G	T	^	G	T		X	G A	G G	G	^	C		A	c	A						G	6	G		T -	G (
5	DRB1-1334		T	G	Ä	G	Ä	G		Ž,	c	c	+	A	G			**	3 A	G	G	A	c		A	c	G					- 1	G G		G		T T	G (
	DRB1-0315		т	G	A	G	A	a			c	G	т	A	G	T		8	з А	G	G	A	c		A	G	A					1	G		6		T	G 1	
	DRB1-1316		T	G	٨	G	A	G		ä	c	G	т	A	G	T			G A	G	G	A	c		A	c	A			G		- 1	G		G		T	G 1	
	DRB1-130101 DRB1-130102		T	G	A	G	A	G			c	G	Ţ	A	G	Ţ			G A		G	A	c		A	C	G						G		G		T	G 1	
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General strategy for medium resolution typing is described below:

For medium resolution typing a maximally informative set of marker positions were determined. These consist of positions 98, 414, 539, 282, 571, 368, 256, 292, 238, 270, 453, 527, 502, 81, 268, 559, 92, 123 and 396 of HLA-A (numbering starts at the transcription start position of exon 1), positions 539, 419, 559, 412, 272, 362, 302, 363, 206, 369, 259, 97, 583, 292, 222, 527, 418, 435 and 571 of HLA-B (numbering starts at the transcription start position of exon 1), and positions 125, 196, 197, 227, 261, 286, 299, 308, 341 and 345 of HLA-DRB1 (numbering starts at the transcription start position of exon 1).

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In general, the order of the positions is from the most informative to the least informative with respect to the selection criteria of frequent and rare HLA alleles (see list of frequent HLA alleles above). Thus the ten markers (HLA-A and HLA-B) that were selected for the fine typing strategy constitute the first ten markers of the set of 19 markers for the single pass classification into frequent and rare HLA alleles (HLA-A and HLA-B). Like with sequence-based HLA typing there are heterozygous combinations of HLA alleles that can not be resolved. However, there are fewer ambiguities with this method due to the mini-haplotypes that are provided.

20. Another object of the present invention is the use of said methodology of the invention is for screening of tissue donors, for example, bone marrow donors in registries for frequent and rare HLA types.

The description of the HLA alleles is based on the Anthony Nolan database (October 25 2003).

In addition to the aforementioned method, the invention includes yet other arrangements which will emerge from the description that follows, which refers to examples of supports according to the invention, as well as the annexed figures and tables, wherein:

Figure 1 describes 19 positions covered by mini-haplotyping assays for discrimination of HLA-A mapped onto the HLA-A allele A*010101 as reference. Black boxes indicate an extension position while grey boxes indicate polymorphisms that are

captured by the annealing of the respective primer of the primer pool. Pools are used in forward and reverse. Numbering is according to the transcription start of the cDNA.

Figure 2 describes 19 positions covered by mini-haplotyping assays for discrimination of HLA-B mapped onto the HLA-B allele B*070201 as reference. Black boxes indicate an extension position while grey boxes indicate polymorphisms that are captured by the annealing of the respective primer of the primer pool. Pools are used in forward and reverse. Numbering is according to the transcription start of the cDNA.

Figure 3 describes 10 positions covered by mini-haplotyping assays for discrimination of HLA-DRB1 mapped onto the HLA-DRB1 allele DRB1*034874 as reference. Black boxes indicate an extension position while grey boxes indicate polymorphisms that are captured by the annealing of the respective primer of the primer pool. Pools are used in forward and reverse. Numbering is according to the transcription start of the cDNA.

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Figure 4 describes 10 positions covered by mini-haplotyping assays for discrimination of HLA-A mapped onto the HLA-A allele A*010101 as reference for the distinction of subgroups that can then be further analysed. Black boxes indicate an extension position while grey boxes indicate polymorphisms that are captured by the annealing of the respective primer of the primer pool. Pools are used in forward and reverse. Numbering is according to the transcription start of the cDNA.

Figure 5 describes 10 positions covered by mini-haplotyping assays for discrimination of HLA-B mapped onto the HLA-B allele B*070201 as reference for the distinction of subgroups that can then be further analysed. Black boxes indicate an extension position while grey boxes indicate polymorphisms that are captured by the annealing of the respective primer of the primer pool. Pools are used in forward and reverse. Numbering is according to the transcription start of the cDNA.

Figure 6 describes Genotyping results of a CEPH family (1418, 01 = father, 02 = mother, 03 = child, 04 = child) for position HLA-B_272. 1407,3 Da corresponds to

the addition of C to primer 6, 7, 8, or 9; 1422,3 Da corresponds to the addition of T to primer 6, 7, 8, or 9; 1431,4 Da/ 1430,9 Da corresponds to the addition of A to primer 6, 7, 8, or 9; and 1447,4 Da/ 1448,5 Da corresponds to the addition of G to primer 6, 7, 8, or 9.

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Table I represents HLA-A alleles captured by the 10 markers in the different subgroups and additional positions that have to be typed to resolve the subgroups.

Table II represents HLA-B alleles captured by the 10 markers in the different subgroups and additional positions that have to be typed to resolve the subgroups.

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Table III represents HLA-DRB1 alleles captured by the 10 markers in the different subgroups and additional positions that have to be typed to resolve the subgroups.

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Table IV represents the list of the individual primers that are required to constitute the pools for mini-haplotyping of HLA-A (19 markers). The 10 markers required for the creation of subgroups are also contained. ^ refers to the base used to attach the mass/charge tag, CT refers to the mass difference of the mass/charge tag, sp means phosphorothioate group. The product analysed by mass spectrometry includes the base 5'of the most 5' sp.

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Table V represents the list of the individual primers that are required to constitute the pools for mini-haplotyping of HLA-B (19 markers). The 10 markers required for the creation of subgroups are also contained. ^ refers to the base used to attach the mass/charge tag, CT refers to the mass difference of the mass/charge tag, sp means phosphorothioate group. The product analysed by mass spectrometry includes the base 5'of the most 5' sp.

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Table VI represents the list of the individual primers that are required to constitute the pools for mini-haplotyping of HLA-DRB1 (10 markers). ^ refers to the base used to attach the mass/charge tag, CT refers to the mass difference of the mass/charge tag, sp means phosphorothioate group. The product analysed by mass spectrometry includes the base 5' of the most 5' sp.

Table VII represents the resolution that can be generated with the 19 markers for the distinction of the frequent HLA alleles in HLA-A.

Table VIII represents the resolution that can be generated with the 19 markers for the distinction of the frequent HLA alleles in HLA-B.

Table IX represents the resolution that can be generated with the 10 markers for the distinction of the frequent HLA alleles in HLA-DRB1.

Table X represents the list of HLA-A alleles that are resolved with the 10 markers for the creation of subgroups. Each subgroup is separated by an empty line. Frequent alleles are shaded in darker grey, while lighter grey indicates the position that primers are extended onto.

Table XI represents the list of HLA-B alleles that are resolved with the 10 markers for the creation of subgroups. Each subgroup is separated by an empty line. Frequent alleles are shaded in darker grey, while lighter grey indicates the position that primers are extended onto.

Table XII represents the list of HLA-DRB1 alleles that are resolved with the 10 markers for the creation of subgroups. Each subgroup is separated by an empty line. Frequent alleles are shaded in darker grey, while lighter grey indicates the position that primers are extended onto.

25 Examples

Example: Mini-haplotyping at position 272 of HLA-B by the modified GOOD-Assay

A locus specific PCR product of exon 2 and exon 3 of HLA-B is amplified with a set of primers published by the International Histocompatibility Working Group, Technical Manuals (Hurly, Fernandes-Vina, Gao, Middleton, Noreen, Ren and Smith; www.ihwg.org/tmanual/Tmcontents.htm). The PCR product is incubated with SAP to remove all excess dNTPs. Then a single base primer extension at position 272 in the PCR amplicon is carried out. The set of primers, to generate the mini-haplotypes is

shown in Table V. Thereafter a 5'phosphodiesterase digest is applied to reduce the primers to a core sequence. After alkylation of the DNA backbone of the minihaplotype fragments the products are transferred onto a MALDI target pre-coated with matrix. Alternatively the matrix solution can be mixed with the samples and transferred onto the MALDI target to dry. The MALDI target is introduced into a MALDI mass spectrometer and analysed. The mass spectra show one or two mass peaks and that correspond to specific mini-haplotypes.

PCR:

Forward primer, BAmp1 5'-G GGT CCC AGT TCT AAA GTC CCC ACG-3'(1.875 pmol), reverse primer, BAmp2 5'-CC ATC CCC GGC GAC CTA TAG GAG ATG-3' (1.875 pmol) an BAmp3 5'-AGG CCA TCC CGG CGG GCG ATC TAT-3' (1.875 pmol), 0.25 μl 10x PCR buffer (HiFi Platinum Taq)), 0.3 μl MgSO₄ (50 mM), 0.2 μl of a mix of each dCTP, dATP, dGTP and dTTP (2 mM each), 0.25U engineered DNA polymerase (HiFi Platinum DNA Polymerase; Invitrogen) and 5 ng DNA fill to 3 ul with water. Cycling: 1. 94°C 3 min, 2. 94°C 20 sec, 3. 64°C 30 sec, 4. 72°C 30 sec, steps 2 to 4 are repeated 35 times, 5. 72°C 5 min.

SAP digest:

20 1.75 μl of 50 mM Tris-HCl and 0.25 μl SAP (USB corporation, Cleveland, USA) are to add to the PCR product and this has to be incubated for 60 min at 37°C, followed by an incubation at 90°C for 10 min to denature the SAP enzyme.

Single Base Primer Extension:

To the SAP treated PCR product 2 ul of an extension mix is to add. This mix contains 15 mM MgCl₂, 0.1 mM of each of the four α-S-ddNTPs, 5 pmol of the extension primers set and 0,4 U of Thermosequenase. Cycling: 1. 94°C 2 min, 2. 94°C 15 sec, 3. 58°C 20 sec, 4. 72°C 20 sec, steps 2 to 4 are repeated 50 times.

30 PDE digest:

To the extension product has to be added 0.5 ul 0.5 M acetic acid and 1.5 ul PDE (5.1U) and incubate for at lease 120 min at 37 °C.

Alkylation:

The alkylation is carried out by adding 21 μl of an alkylation mix and incubate for 15 min at 40°C. This mix contains 377 parts water free acetonitrile, 15 part 2M triethylamine/CO₂ (pH ~7.5), 75 parts 2mM Tris-HCl and 174 parts methyljodate.

5 The alkylation is to stop by adding 10 μl deionisated water. 5 μl of the resulted upper phase are to dilute in 10 μl 40% acetonitrile.

For MALDI target preparation and measurement with the MALDI mass spectrometer 0.5 μl of the final dilution are transferred onto a MALDI target pre-coated with matrix (α-cyano-4-hydroxycinnamic acid methyl ester). Measurement was carried out in a Bruker Autoflex with typically 18 kV acceleration voltage, pulsed ion extraction with a delay of 200 ns, and detection in linear detection mode. Results for CEPH family 1418 are shown in figure 6.

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Claims

1. Method for HLA typing by the unambiguous determination of short DNA sequence elements (2-6 bases) at a given position simultaneously on both parental alleles at a selected number of positions in HLA genes, comprised of the steps for each position of a) hybridising a combination of oligonucleotides (primers) complementary to all known sequence variants to a DNA strand upstream of a given position; b) carrying out a primer extension reaction with at least one of the four dNTP substrates substituted by a terminating analog; c) analysing the products by mass spectrometry, with the resulting masses allowing unambiguous identification of the used primers and the added bases.

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- 2. Method according to claim 1 where the DNA strand of step a) is produced by a DNA replication procedure such as PCR or rolling circle replication.
- 3. Method according to claim 1 where the combination of primers has slightly varying sequences so that all sequences of the haplotypes are represented by a perfectly matching primer.
 - 4. Method according to claim 3 where mass shifting tags are added to the individual primers sequences to make them uniquely distinguishable once the terminating base is added.
- 5. Method according to claim 1 where distinguishable termination products for known alleles are generated by extending the perfectly hybridised primer with a combination of dNTPs and ddNTPs or analogs thereof with a DNA polymerase to generate specific termination products.
 - 6. Method according to claim 1 where the GOOD assay is used.
- 25 7: Method according to any of the precedent claims where mass spectrometry, in particular MALDI or ESI mass spectrometry is used for analysis of the masses of products.
 - 8. Method for HLA typing according to any of the precedent claims above where set of multiple selected positions are queried to achieve sufficient information content.
 - 9. Method for HLA typing of HLA-A according to claims 1-8 where assays of the positions 98, 414, 539, 282, 571, 368, 256, 292, 238, 270, 453, 527, 502, 81, 268, 559, 92, 123 and 396 (according to the numbering of the HLA-A gene starting at cDNA sequence position 1 of exon 1) are used to achieve medium resolution.

10. Method for HLA typing of HLA-B according to claims 1-8 where assays of the positions: 539, 419, 559, 412, 272, 362, 302, 363, 206, 369, 259, 97, 583, 292, 222, 527, 418, 435 and 571 (according to the numbering of the HLA-B gene starting at cDNA sequence position 1 of exon 1) are used to achieve medium resolution.

- 11. Method for HLA typing of HLA-DRB1 according to claims 1-8 where assays of the positions 125, 196, 197, 227, 261, 286, 299, 308, 341 and 345 (according to the numbering of the HLA-DRB1 gene starting at cDNA sequence position 1 of exon 1) are used to achieve medium resolution.
- 12. Method for HLA typing of HLA-A according to claims 1-8 where assays of the positions 98, 414, 539, 282, 571, 368, 256, 292, 238 and 270 (according to the numbering of the HLA-B gene starting at cDNA sequence position 1 of exon 1) are used to generate subgroups A-O.
- 13. Method for HLA typing according to claim 12 where assays of the positions 224, 15 268, 376, 502, 561 and 616 are preferably analysed to resolve subgroup HLA-A_A; positions 126 and 526 to resolve subgroup HLA-A B; positions 81, 90, 92, 212, 214, 257, 265, 299, 302, 404, 420, 427, 453, 485, 489 and 502 to resolve subgroup HLA-A_C; positions 160, 200, 362 and 524 to resolve subgroup HLA-A_D; positions 180, 299, 301, 302, 346, 418, 453, 517, 524, 526, 527, 557, 559 and 560 to resolve subgroup HLA-A E; positions 299, 301, 302, 341 and 583 to 20 resolve subgroup HLA-A_F; positions 127, 341, 399, 480, 502, 503, 524, 526, 527, 553, 559, 560 and 565 to resolve subgroup HLA-A_G; positions 228, 233, 463, 519, 530 and 583 to resolve subgroup HLA-A_H; positions 102, 275, 317, 362, 418, 419, 497, 524, 555, 595 and 618 to resolve subgroup HLA-A_I; 25 positions 92, 331, 453, 524, 559, 560 and 564 to resolve subgroup HLA-A J; positions 78, 81, 123, 125, 142, 144, 194, 268, 294, 324, 355, 362, 396, 403, 419, 453, 456, 477, 493, 517, 524, 526, 527, 559 and 560 to resolve subgroup HLA-A_K; positions 113, 299, 301, 302, 308, 311, 523, 524 to resolve subgroup HLA-A_L; positions 171, 363, 498 and 559 to resolve subgroup HLA-A M; positions 30 376, 426, 527, 555, 557 and 595 to resolve subgroup HLA-A N; position 299 to resolve subgroup HLA-A O are used.
 - 14. Method for HLA typing of HLA-B according to claims 1-8 where assays of the positions 539, 419, 559, 412, 272, 362, 302, 363, 206 and 369 (according to the

numbering of the HLA-B gene starting at DNA sequence position 1 of exon 1) are used to generate subgroups A-AC.

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- 15. Method for HLA typing according to claim 14 where assays of the positions 259, 341 and 473 are preferably analyzed to resolve subgroup HLA-B A; positions 106, 144, 222, 259, 273, 311, 313, 418, 445, 493, 528 and 540 to resolve subgroup HLA-B B; positions 319, 416, 545 and 572 to resolve subgroup HLA-B C; positions 106, 131, 165, 215, 243, 277, 292, 322, 481, 582, 603 and 616 to resolve subgroup HLA-B_D; positions 106, 146, 165, 181, 238, 259, 263, 292, 328.1/329, 379, 435, 453, 463, 485, 526, 571, 572 and 583 to resolve subgroup HLA-B E; positions 142, 171, 255, 257, 395, 430, 544, 566 and 572 to resolve subgroup HLA-B_F; positions 117, 247, 248, 277, 345, 418, 489 and 527 to resolve subgroup HLA-B_G; positions 134, 141, 200, 213, 259, 304 and 527 to resolve subgroup HLA-B_H; positions 83, 141, 211, 222, 242, 322, 404, 414, 435, 463, 502, 527, 544, 571, 572 and 583 to resolve subgroup HLA-B_I; positions 103, 142, 222, 243, 259, 292, 477, 486 and 499 to resolve subgroup HLA-B J: positions 103, 259, 292, 295, 527 and 583 to resolve subgroup HLA-B K; positions 320 and 500 to resolve subgroup HLA-B_L; positions 311, 527 and 583 to resolve subgroup HLA-B_M; positions 119, 292, 259, 319, 425, 527, 546 and 583 to resolve subgroup HLA-B_N; positions 97, 142, 245 and 527 to resolve subgroup HLA-B_O; positions 97 and 175 to resolve subgroup HLA-B P; positions 246 and 277 to resolve subgroup HLA-B_Q; positions 246, 292, 311 and 503 to resolve subgroup HLA-B_R; positions 103, 261, 309, 311 and 474 to resolve subgroup HLA-B_S; positions 97, 103, 106, 243, 259, 292, 404 and 524 to resolve subgroup HLA-B_T; positions 259 and 320 to resolve subgroup HLA-B_U; position 106 to resolve HLA-B_V; positions 97 to resolve HLA-B W; positions 97, 106, 257, 418 and 463 to resolve HLA-B_X; position 106 to resolve HLA-B_Y; positions 106 and 144 to resolve HLA-B_Z; positions 117, 247, 248, 283, 345, 418, 489, and 527 to resolve HLA-B_AA; positions 106 to resolve HLA-B_AB; positions 548 to resolve HLA-B_AC.
- 30 16. Method of HLA typing according to claim 11 to resolve subgroups A-P of HLA-DRB1.
 - 17. Method for HLA typing according to claim 16 where assays of the positions 123, 174, 250, 278 and 317 are analysed to resolve subgroup HLA-DRB1_A; positions 192, 203, 256 and 259 to resolve subgroup HLA-DRB1_B; 256, 260, 317 and 351

to resolve subgroup HLA-DRB1_C; positions 155, 204, 233, 239, 256, 304, 357 and 366 to resolve subgroup HLA-DRB1_D; positions 122, 171, 257 and 317 to resolve subgroup HLA-DRB1_E; positions 164, 167, 171, 230, 235, 306, 317, 321 and 337 to resolve subgroup HLA-DRB1_F; positions 164, 257, 266 and 303 to resolve subgroup HLA-DRB1_G; positions 164, 181, 188, 220, 229, 256, 266, 317 and 318 to resolve subgroup HLA-DRB1_H; position 257 to resolve subgroup HLA-DRB1_I; positions 181, 239 and 357 to resolve subgroup HLA-DRB1_J; positions 122, 144, 239, 303, 317, 318 and 321 to resolve subgroup HLA-DRB1_K; positions 118, 161, 257, 260, 318 and 321 to resolve subgroup HLA-DRB1_L; positions 165, 257, 293 and 303 to resolve subgroup HLA-DRB1_N; positions 177, 240, 256, 257 and 357 to resolve subgroup HLA-DRB1_N; positions 150 175, 230, 236 and 321 to resolve subgroup HLA-DRB1_O; positions 115, 220 and 317 to resolve subgroup HLA-DRB1_O; positions 115, 220 and 317 to resolve subgroup HLA-DRB1_P are used.

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- 18. Kit for the implementation of the procedure according to claims 1 17 comprising pools of primers.
 - 19. Use of the method according to claims 1-17 for screening of tissue donors.
 - 20. Use according to claim 19 for bone marrow donors in registries for screening of frequent and rare HLA types.
- 20 21. Use of the primers represented in Table IV, V and VI to carry out HLA typing.

Abstract

Method for HLA typing

A method for the identification of DNA sequence elements in complex and highly variable sequences is described. The method consists of identifying a short sequence element of several DNA bases (2-6 bases) at a given position in the genome simultaneously on all parental alleles. The method allows differentiating mini-haplotypes on different alleles in one analysis. The method consists of carrying out an enzymatic primer extension reaction with a combination of extension primers (pool of primers) and analysing the products by mass spectrometry. The pool of primers is assembled in such a way that the primer extension product allows unambiguous identification of both the primer of the pool that was extended and the base that was added. The method is of great utility for DNA sequences harbouring many SNPs close to each other with many possible haplotypes. Such sequences are known in the Major Histocompatibility Complex (MHC). This method is particularly well suited for DNA-based HLA typing and in combination with a suitable selection of sites tested, it is superior in ease of operation to conventional HLA typing methods. We have identified sets of these assays for HLA-A, HLA-B, and HLA-DRB1 that allow unambiguous four-digit HLA of each of these genes with between 11 and 28 queried markers.

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ATCCGTGTCCCGGCCCGGCCGGCGGGCCCCCCCCTTCATCGCCGTGGGCTACGTGGACGACGAGTTCGTGCGGTTCGACAGGGGCGCCGCGAGGCCAGAAGATGGAGCCGCGGG

559 571 AGGGO<mark>GGI</mark>GCGI<mark>GGAGG</mark>GGCTCCGCAGATACCTGGAGAAGGGAAGGAGGACGCTGCAGGGGTACCAGGGGGCCACGGGGCGCCTCCCTGATCGCCTATAGATCTCCCGGGC

*453 TACATCGCCCTGAA<mark>GAA</mark>GACCTGCGCTCTTGGACGGGGGGGGGGACATGGCAGTCACA<mark>MAGCO</mark>CAAGTGGGAGGCGGTCC<u>MTG</u>GGCGGAGAAGAGAGTCTACCTGG

TGGCCTCCCAC

ATGGCCGTCATGGCGCCCCCGAACCCTCCTCCTGCTACTCTCGGGGGCCCTGACCCTGACCCAGACCTGGGCGGGTGAGTGCGGGGTCGGGAAAACC<u>GGGRGGGGGGGGGGGGGGGG</u>

*123 ATCCGTGTCCCGGCCGGCGGGGGGTTCATCGCCGTGGGCTACGTGGACGACACGCAGTTCGTGCGGTTCGACAGCGACGCGGGAGCAAGAAGATGAAGCGCGGGG 数照数6GGCCCTCCTGGCGGGGGCGCAGGACCGGGGAGCCGCGGGAGGAGGAGGGTCGGGCAGGTCTCAGCCACTGCTCGCCCCCAGGGTAGTCCATGATAT

· _-- -

*238 *256 262* CGCCGTGGATAGAGCAGG<u>SSS</u>GGGAGTATTGGGAC<mark>OSGG</mark>AGACA<mark>SGGAATSTG</mark>AAGGGCCAAGCCAGGAACCTGGGGGACCCTGCGCGGCTACTACAACCA

* 502 TACATCGCCCTGAA<mark>GGAG</mark>GACCTGCGCTCTTGGACGCGGGGCGGCGGACATGGCTCCAGATCACCA<mark>AGCG</mark>CAAGTGGGAGGCGGTCCAA<mark>AGAG</mark>GAGAGTCTACCTGG 368* GACCGC*GGGGTCGGGGTTCTCACACCATCCAGATAA<mark>TGMA</mark>TGGCTGCGACGTGGGGCCGGACGGGG<mark>MT</mark>MGTCCGCGGGTA<mark>@MG</mark>CAGGACGCCTACGACGGCAAGGAT*

57<u>1</u>* |<u>GGARGE</u>GGCTCCGCAGATACCTGGAGAACGGAAGGAAGGAGCCCTGCACGGGTACCAGGGGCCACGGGGCGCCTCCCTGATCGCCTATAGATCTCCCGGGC

TGGCCTCCCACHINE HER CONTROLL OF THE CACACTAGAATATCACCCTCCTG

FIGURE 2

FIGURE 3

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(]:

CTAGAGAAGCCAATCAGCGTCGCCG<u>BABBBBBBBBBBBBBBB</u>CACCCACCCGGACTCAGAGTCTCCTCAGACGCCGAGA*TGCTGGTCATGGCGCCCCGAACCGTCTC* crectectc

206* *222 CTTCATCTCAGTGGGCTACGTGGACGACACCCAGTTCGACACGCGACGCCGCGAGTCCGA<mark>CAA</mark>GGAGCCGCGGGGGCGCCG<mark>GTGG</mark>ATAGAGCAGGAGGGGCCGGAGTAT

CGCAGGTCACGACTCCCCCATACGGCCCGGGTCGCCCGAGTCTCTCCGGGTCCGAGATCCGCCTCCCTGAGGCCGGGGACCCGCCAAGACCTCGACCGGCGAGAGCC

435 ACCCTd<u>CA短角GOA開</u>GTA<mark>GGGG</mark>TGCGACGGGGGGGGGGGGGGGGGGGGAAGGAAGGAACGAAGGAATTACATCGCCCTGAACGACCTGCGCT 412 418**419 *369 362**363

527* *539* *559 *571 CCTGGACCGCGGACACGGGGTCAGTCACCCAGGGCAAGTGGGAGGGGGCGCCG<mark>GTGA</mark>GGCGGAGG<mark>AGGG</mark>GAGAGCCTACCTGGAGGGGC<mark>GAGT</mark>GCGTGGAG<mark>TIGG</mark>TTCCGCAG

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CTAGAGAAGCCAATCAGCGTCGCCG**MENERINGENERINGENERINGE**CACCCACCCGGACTCAGAGTCTCCTCAGACGCCGAGA*TGCTGGTCATGGCGCCCCCGAACCGTCCTC* crectect corgect corgeneral constances and the constance of the constan

206* CITCAICICAGIGGCIACGIGGACACACCCAGITCGIGAGGITCGACACGCGAGCCGCGAGICCGA<mark>GAGA</mark>GGAGCCGCGGGCGCCGIGGAIAGAGCAGGAGGGGCCGGAGIAI

CGCAGGTCACGACTCCCCCACGTACGGCCCCGGGTCGCCCGAGTCTCCGGGTCCGAGATCCGCCTCCTGAGGCCGGGGACCCGCCCAGACCCTCGACCGGCGAGAGCC

362**363 *369 ACCCTC<u>CA愛教**GG**AM</u>GTA**GGG**TGCGACGGGCGCGCGCCCTCCTCCGCGG<mark>MAMG</mark>ACCAGTAMGCGTACGCCAAGGATTACATCGCCCTGAACGAGCACCTGCGCT

539* CCTGGACCGCCGCACACGCGCTCAGATCACCCCAGCGCAAGTGGGAGGCGGCCGTGAGGCGGAGGAAGGGCTACCTGGAGGGGG<mark>AMGT</mark>GCGTGGAGTGGCTCCGCAG

a*tacciggagaacggaaggacaagciggagcggcig*gtaccagggagigggggagigggggcacticcc**ggggggg**gg

€.

227* *308 *308 *308 *308 *308 *308 *261 *261 *261 *261 *262 * 286* 286* 286* 286* 286* *308

MARCONDENSION OF CAGOTEAGCGCGCGCGCGGGGCCTGAGTCCCTGTGAGAA 341* *345 CTACTGCAGACACAACTACG<mark>GGGH</mark>TGG<mark>HGAG</mark>

FIGURE

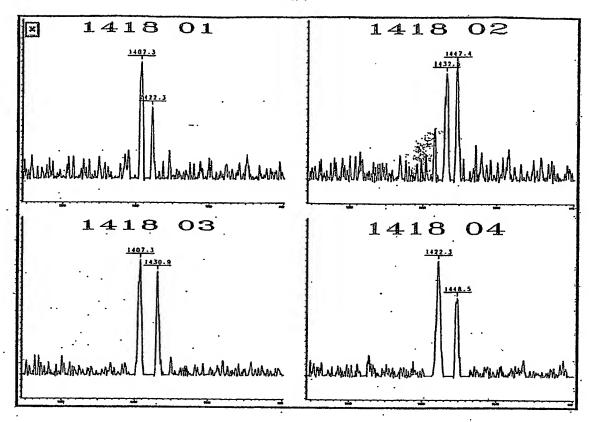


FIGURE 6